# Exhibit E

**UNITED STATES DISTRICT COURT**
**SOUTHERN DISTRICT OF WEST VIRGINIA**
**AT CHARLESTON**

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| **IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION**<br><br>**THIS DOCUMENT RELATES TO WAVE 1** | **Master File No. 2:12-MD-02327**<br><br>**JOSEPH R. GOODWIN**<br>**U.S. DISTRICT JUDGE** |

# RULE 26 EXPERT REPORT OF DR. PEGGY PENCE

**PEGGY PENCE, PhD, RAC, FRAPS**
**EXPERT WITNESS REPORT**

**ETHICON, INC., ETHICON WOMEN'S HEALTH AND UROLOGY, a Division of Ethicon, Inc., GYNECARE, AND JOHNSON & JOHNSON**
**(Collectively referred to in this Report as Ethicon)**

# I. CREDENTIALS AND METHODOLOGY

## A. Credentials: Qualifications and Experience

I have more than 40 years of experience in the research and development of traditional pharmaceuticals, biotechnology-derived therapeutics (biopharmaceuticals), and medical devices, including in vitro diagnostics. I began my career at Eli Lilly and Company in 1970 in basic immunology research and later transitioned to clinical and regulatory affairs. I subsequently held project management and clinical management positions, from 1983 to 1992, at a number of emerging-growth companies, including Serono Laboratories (U.S. start-up), Triton Biosciences (acquired by Berlex Laboratories, Inc.), and Amgen, Inc.

In 1992, I founded a consulting firm that was incorporated in 1995 as Symbion Research International, Inc., a full-service contract research organization (CRO) and consulting firm. I have been President and Chief Executive Officer since that time. In this position, I provide advice, guidance, and product development services to pharmaceutical/biopharmaceutical and medical device companies in the areas of strategic planning, preclinical testing, clinical trials design and conduct, and regulatory matters involving the U.S. Food and Drug Administration (FDA), as further discussed below.

Over the course of my career, I have worked with more than 80 companies and over 90 medical devices, pharmaceuticals (drugs), and biopharmaceuticals (biologic therapeutics), including combination products (e.g., device-drug combination products). I have guided and coordinated product development activities from manufacturing process development through marketing plans and have led development programs for a number of novel therapeutics and medical devices. My medical device experience encompasses all Classes of medical devices: Classes I, II and III. I have broad experience spanning multiple therapeutic areas, including women's health, neurology, neuropsychology, oncology, hematology, infectious disease, rheumatology, nephrology, respiratory disorders, metabolic and growth disorders, gastroenterology, burns, wound healing, and ophthalmology. As regards women's health and wound healing and of particular relevance to the subject matter of this Report, I have designed clinical trials for diseases of the female genital system and have been involved in both preclinical and/or clinical testing of novel medical devices and biologics for wound healing applications, including both deep wounds and surgical incisions.

Notably, the product materials I have reviewed for this Report are the same types of materials I have either prepared or reviewed to assure their accuracy, completeness, and regulatory compliance during the course of my professional career. Further, Ethicon's responsibilities about which I have opined are the same types of responsibilities I have executed over the course of my career in medical product development. I have been an integral or leading member of multiple product development teams to determine the testing requirements for medical devices and drugs/biologics and to make decisions concerning whether additional testing and, if so, what types of additional testing were needed based on initial results of product testing. I have advised manufacturers on the adequacy of proposed medical device labeling. I have also contributed substantially to the development and content of product labeling, including for medical devices. For example, I have prepared clinical study reports and summarized key findings, including safety information, for inclusion in labeling. Further, I have written a number of Investigator's Brochures, which have been termed proto-labeling, because the Investigator's Brochure is the premarketing forerunner of the product package insert and provides the same types of information as the package insert, including adverse reactions, contraindications, warnings and precautions, to advise physicians and other healthcare practitioners of information important to their safe and effective use of medical products. I have analyzed safety information available from clinical trials, the scientific and medical literature, and postmarketing experience to provide this information to the U.S. Food and Drug Information (FDA) and to physicians and other healthcare practitioners to enable their safe and effective use of medical devices and drugs/biologics. I have submitted safety alerts to FDA and physicians about new and important product safety information.

Additionally, I have prepared marketing materials detailing product information. In so doing, I assured the accuracy and fair balance of the safety and effectiveness information presented. Similarly, I have advised companies on the appropriateness of information in press releases and other corporate documents to ensure any potentially misleading or improper information was excluded.

The above is a brief overview of my professional experience relevant to this Report. Further details are described below.

I have performed due diligence evaluations of potential new products to advise sponsor companies or research institutes on product development requirements, including preclinical and clinical testing needs and also regulatory pathway and strategy. I have managed internal and extramural preclinical research programs required for support of product development and manufacturing, clinical research, and business development activities. These have included product characterization, process improvement, stability studies, bioassay development, pharmacology, and preclinical efficacy studies. Additionally, I have developed product-specific, preclinical toxicology testing plans and protocols and have overseen the conduct and reporting of these studies for FDA-regulated products. I have taught Good Laboratory Practice (GLP), which is the regulatory standard for conducting nonclinical (preclinical) laboratory studies to support applications submitted to FDA for research or marketing authorizations. In addition, I have conducted GLP audits of toxicology testing facilities.

Evaluation of preclinical safety and efficacy data are central considerations before initiating human use. Accordingly, I have designed clinical investigational plans and clinical protocols in consideration of preclinical study results, including both efficacy and toxicology data. As a key member of many product development teams, I have been instrumental in the assessment of

preclinical data to determine whether the available safety information supported the transition from preclinical to clinical use. Similarly, I have evaluated both preclinical and available clinical safety data to determine whether product safety profiles supported application for marketing authorization and also product development for new clinical uses.

I have designed and managed or directed the conduct of numerous clinical studies, from first-in-man studies of novel therapeutics and medical devices to pivotal studies for marketing approval. This has included performing and/or directing the monitoring, data management, analysis, and reporting of the safety and effectiveness/efficacy data from these studies, ensuring that all activities were performed in compliance with applicable regulations, Good Clinical Practice (GCP), the international regulatory and quality standard for the conduct of clinical trials involving human subjects and other relevant FDA Guidances. Of note, I established, staffed, and directed the first Clinical Quality Assurance and Document Control department at Amgen, a leading biotechnology firm. Further, I have directed collaborative clinical programs with foreign affiliates to reduce overall clinical development time and costs, and enhance quality and usability of data globally for marketing applications.

I have organized and directed meetings of clinical study physicians ("investigators") at the outset of multicenter clinical trials both to obtain concurrence on complex clinical study designs and endpoints and also to instruct these physician investigators on clinical trial requirements and their obligations to comply with the clinical study protocol, all applicable regulations, and GCP. I have performed compliance (quality assurance) audits of clinical investigators' conduct of clinical trials and advised and worked with them and their clinical study staff to correct any deficiencies identified. With respect to FDA inspections of clinical studies, I have been the sponsor representative with lead responsibility for "hosting" the FDA inspection of a sponsor company and clinical investigative sites.

I have provided consultation to multiple companies to establish or evaluate their processes and procedures and, in the latter case, to implement changes necessary to achieve compliance with regulatory and industry standards. In this role, I have developed standard operating procedures and set up operations to perform all aspects of clinical studies and regulatory affairs, including the following activities, among others: clinical protocol design; writing patient informed consent forms (including all known or potential risk information); writing investigator's brochures or report of prior investigations (the forerunner of the package insert/professional labeling); clinical study monitoring and management; data tracking and management; recordkeeping; and reporting of adverse events. Such procedures at Symbion have undergone quality assurance audits by multiple sponsor companies successfully. Further, I have consulted with a multinational pharmaceutical company both to develop implementation strategy and also to implement a global clinical data management system.

I have managed coding of adverse events (using dictionaries designated for regulatory activities) for worldwide clinical programs for the purpose of safety evaluations and regulatory reporting and have collected, investigated, evaluated, and reported safety data to fulfill both premarketing and postmarketing regulatory obligations. I have advised physician investigators of updated safety information: (i) in the context of providing updated investigator's brochures (which contain similar contents as eventual, professional product labeling [to the extent of known information], in order to provide for safe and effective use of the investigational product); and (ii) through required serious adverse event reports to advise physicians (as well as FDA) of new, critical safety information concerning serious risks with use of the investigational

product. In the postmarketing setting, I also have directed the updating of postmarketing surveillance procedures and audited postmarketing adverse reaction records for regulatory compliance. Additionally, I have evaluated post-marketing utilization data.

I have reviewed or contributed substantially to the development of product labeling, including not only adverse reaction content but also contraindications and warnings, nonclinical toxicology and clinical studies information, and product use instructions. I have prepared product launch "backgrounders" for marketing programs and critically reviewed press releases of sponsor companies and other corporate documents prior to their release to ensure any potentially misleading or improper information is excluded.

I have served as the U.S. Agent or authorized representative for FDA matters for both medical device and drug companies, with responsibility for FDA communications and, in the case of medical device companies, for establishment registration and device listing. I have prepared and made numerous regulatory submissions of multiple types to FDA, including premarketing and postmarketing submissions, both for medical devices and drugs/biologics. Additionally, I have advised sponsor companies regarding a broad scope of regulatory requirements, including adverse event reporting, the content of adverse reactions in labels and corrective and preventive actions to address FDA inspectional findings. I have represented sponsor companies during many face-to-face meetings and teleconferences with FDA.I have served on the Board of Directors or Advisory Board for multiple organizations, including the Biotechnology and Health Programs Advisory Board, California State University Channel Islands (CSUCI); the Clinical Trials Certificate Program Advisory Board, California State University Program for Education and Research in Biotechnology (CSUPERB); and CompassioNow (formerly CareNow Foundation, the purpose of which is to provide medical care to the world's least served). At CSUCI, I also have served as an Advisor for the Master of Science in Biotechnology (MS Biotech) team projects, a curriculum requirement in an academic or industrial location. I have developed and teach a graduate level course titled "Clinical Trials and Quality Assurance" in the CSUCI MS Biotech program curriculum. As part of this course, I instruct my students on ethics in medical product development and the importance of obtaining and evaluating adequate preclinical safety data before transitioning to human use and assign them case studies relevant to this topic for critical evaluation and class presentation. Additionally, I have developed and taught a course titled "Clinical Trials Project Management: Managing Clinical Trials" for graduate level students enrolled in either the Program for Applied Biotechnology Studies or the Certificate in Clinical Trials Project Management Program at California State University, Fullerton. I also have served as guest lecturer for the MS Biotech program, CSUCI.

I have often been an invited speaker at industry conferences or workshops on topics current to the development of medical devices, drugs and biologics and have often provided instruction on Good Clinical Practice and other medical product development topics: at sponsor-company, in-house training programs; workshops and seminars; as a guest lecturer and instructor in university graduate or professional programs (as discussed above). I founded the Drug Information Association (DIA) Sub-group and Advisory Committee on Biotechnology and chaired DIA workshops on biotechnology in 1991 and thereafter from 1993 annually through 2001. I have served on the Regulatory Training Course Faculty for the Drug Information Association. I have been an instructor on the medical device premarketing regulations (2008-2009) and postmarketing regulations (2009) for the Orange County Regulatory Affairs Discussion Group (OCRA) course for regulatory professionals preparing to take the U.S. Regulatory Affairs Certification (RAC) examination.

I am RAC-certified, which means I hold the U.S. Regulatory Affairs Certification (RAC, certifying knowledge of U.S. regulations). The RAC credential is the only certification specifically for regulatory professionals in the healthcare product sector. It is conferred by the Regulatory Affairs Professional Society (RAPS) upon successful performance on a standardized proficiency exam, and in consideration of the applicant's education, training, and overall experience. Continuing education and assumption of leadership roles in the profession are necessary to maintain recertification, which is granted every three years, upon submission of appropriate justification. In addition to maintaining the RAC credential, in 2009 I was named a RAPS Fellow (FRAPS), a peer-reviewed credential that recognizes senior regulatory professionals based on experience, contributions, and leadership in the regulatory profession.

In sum, I have the peer-reviewed qualifications of a RAPS Fellow based on professional experience, credentials, and training. Being RAPS certified[1] and a RAPS Fellow,[2] I have achieved the highest level experience within my profession, Level IV, as outlined in the Regulatory Affairs Professional Development Framework.[3]

I earned a Bachelor of Science degree, *magna cum laude*, in Microbiology from Louisiana Polytechnic University (commonly known as Louisiana Tech) and a Doctor of Philosophy (PhD) degree in Toxicology, with a Pharmacology minor, from Indiana University (Medical School campus). I performed my doctoral research predominantly at the Eli Lilly Laboratory for Clinical Research in Indianapolis, Indiana. My doctoral research included the planning and hands-on conduct of all aspects of three clinical pharmacology and toxicology studies. As the prior valedictorian for my high school, I was recognized in 2008 for my career accomplishments by induction to the Bossier High School Alumni Hall of Fame.

A copy of my current Curriculum Vitae is attached as Exhibit 2.

**B. Methodology**

I have been asked to address the actions of Ethicon, Inc., Ethicon Women's Health and Urology, a Division of Ethicon, Inc., Gynecare, and Johnson & Johnson (collectively referred to as Ethicon) in the context of the company's regulatory responsibilities as the manufacturer of the medical device GYNECARE PROSIMA Pelvic Floor Repair Systems (referred to as PROSIMA or PROSIMA System[s]), indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor, either as mechanical support or bridging material for the fascial defect. The Systems provide maintenance of the vaginal canal during the period of healing following surgical repair of vaginal wall prolapse, while supporting the position of the Mesh Implants. All of my opinions expressed in this Report are offered to a reasonable degree

[1] I tested for and achieved RAPS's Regulatory Affairs Certification ("RAC"). The development of the RAC examination and selection process was based upon extensive research on the scope of practice and specific activities of the profession. This research has been replicated and updated several times, with studies extended to professionals involved with the European, US, and Canadian regulatory systems.

[2] The program recognizes professionals with over 15 years of regulatory experience for their significant contributions and leadership. Fellows receive a prestigious status and serve as important resources for strategic dialogue, mentoring, implementation of special initiatives, and international development. RAPS Fellows, *available at* http://www.raps.org/membership-amp-benefits/raps-fellows.aspx (last visited Feb. 24, 2012).

[3] The Regulatory Affairs Professional Development Framework offers a model for describing the basic body of knowledge and relevant skills of the RA profession across product lines, geographic locations and employer types at four major career stages. The skills, knowledge, and experience that I provide are reflected in this research-driven whitepaper.

of scientific and professional certainty.

During the preparation of this Report, I reviewed, consulted, and relied upon the following categories of information, listed in Exhibit 3:

a) Applicable statutes, regulations, industry standards and guidance documents (See Exhibit 1);
b) Premarket notification 510(k) number K063562 and related Ethicon and FDA correspondence;
c) Other 510(k)s or 510(k) Summaries relevant to the PROSIMA product development history;
d) Other Ethicon documents of multiple types produced in this litigation;
e) Documents located by specifically directed independent on-line searches;
f) Relevant scientific and medical literature (See Exhibit 3);
g) Deposition and trial transcripts (and exhibits); and
h) Ethicon website;
i) FDA website, including the searchable 510(k) database; the Manufacturer and User Facility Device Experience Database (MAUDE) for reports of serious adverse events; FDA's advisories and actions to address the safety issues associated with transvaginal mesh products for pelvic organ prolapse, e.g., FDA's 2008 *Public Health Notification*, 2011 *Safety Communication*, and 2011 Medical Devices Advisory Committee meeting of the Obstetrics and Gynecology Medical Devices Panel; and the 522 Postmarket Surveillance Studies webpages.

A number of these documents are cited in footnotes throughout this Report as primary reference materials.

In reaching my opinions, based on my review, critical evaluation, synthesis, integration, and analysis of the body of relevant evidence, I brought to bear my educational background, professional training, and experience in the fields of regulatory affairs and medical product research and development, including nonclinical and clinical testing to determine medical product safety and efficacy and the monitoring and oversight of compliance with applicable industry standards. I also drew upon the real world lessons learned from my industry experience.

The methodology I employed and level of scrutiny applied to the totality of the evidence in this matter and in the preparation of this Report are no different than those used in my practice over the course of my career as an expert in regulatory affairs, medical product research and development, including the testing and evaluation of medical product safety and efficacy, and as a researcher, educator, and scientist in general. Essentially, I conducted background research, constructed theories, tested those theories against the information I reviewed and the industry standards of which I am aware through my knowledge, experience, and training, analyzed my findings, and communicated my conclusions herein.

I conducted comprehensive observations and analysis of the totality of the categories of information listed above. I employed logical reasoning to my findings and formed conclusions, which are validated by information in the documentation and deposition records. I drew conclusions from my observations based on my extensive and specialized experience. My opinions are grounded in well-established techniques, processes, and methods. They reflect practices undertaken in the medical device industry within the context of the applicable industry

standards that inform and guide industry conduct.

## II. APPLICABLE INDUSTRY STANDARDS (Attached as Exhibit 1 and incorporated as if set forth fully herein)

## III. BACKGROUND UNDERLYING OPINIONS

### A. CLINICAL BACKGROUND: REPAIR OF PELVIC ORGAN PROLAPSE (POP)

#### 1. POP Overview

Pelvic organ prolapse (POP) is a condition that occurs when the pelvic floor tissues that hold the pelvic organs in place become weakened or stretched, often from childbirth. This causes the pelvic organs to bulge (or prolapse) into the vagina. The pelvic organs sometimes prolapse past the vaginal opening, and more than one pelvic organ can prolapse at the same time. The organs involved in POP may include the bladder (cystocele), the uterus (procidentia), the rectum (rectocele), the top of the vagina (apical prolapse) or the bowel (enterocele). POP can be asymptomatic for some women, but for others it may negatively impact the quality of life by causing pelvic discomfort and interfering with sexual, urinary and defecatory function, as well as other daily activities. It is estimated that 10 to 30 per 100,000 women will require surgical intervention and of these, approximately 30% will require additional surgery for recurrence and/or incontinence.

Traditional treatment options for pelvic organ prolapse (POP) include hysterectomy, colporrhaphy (plication of pubocervical or rectovaginal fascia), sacrocolpopexy (suturing of vaginal apex to the sacral promontory using either mesh or fascial bridge) performed either abdominally or laparoscopically, and sacrospinous fixation (securing the vaginal apex to the sacrospinous ligament). Mesh products were introduced as supporting materials in the surgical treatment of POP with the aim of reducing the recurrence rates associated with traditional repairs.

In the 1970s, gynecologists began using surgical mesh products indicated for hernia repair (for which such products had been used since the 1950s) for abdominal repair of POP, and in the 1990s, gynecologists began using surgical mesh for transvaginal repair of POP. Initially, surgeons cut stand-alone mesh to the desired shape and placed it via an abdominal or transvaginal procedure. Subsequently, pre-shaped mesh kits were developed for placement of a mesh implant via a transvaginal procedure. These kits included tools to aid in the delivery and insertion of the mesh.

It is important to note that the first surgical mesh indicated for POP repair became available for sale in 2002, based on its comparative assessment and similarity, i.e., substantial equivalence, to previously legally marketed surgical mesh devices, termed “predicates,” that were indicated for hernia repair. The marketing of this product was not supported by indication-specific clinical data. Similarly, many subsequent mesh products for POP repair have been marketed without supporting clinical data.[4]

[4] Committee Opinion Number 513, Committee on Gynecologic Practice, The American College of Obstetricians and Gynecologists. Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse, December 2011.

Surgical mesh materials can be divided into four general categories:

- non-absorbable synthetic (e.g., polypropylene or polyester)
- absorbable synthetic (e.g., poly(lactic-co-glycolic acid) or poly(caprolactone))
- biologic (e.g., acellular collagen derived from bovine or porcine sources)
- composite (i.e., a combination of any of the previous three categories).

Prosima mesh is comprised of GYNECARE GYNEMESH PS Nonabsorbable Prolene (polypropylene) Soft Mesh.

As noted above, the purpose of implanting surgical mesh is to increase the longevity of POP repairs. In general, mesh products for POP repair are configured to match the anatomical defect they are designed to correct. Mesh can be placed in the anterior vaginal wall to aid in the correction of cystocele (anterior repair), in the posterior vaginal wall to aid in correction of rectocele (posterior repair), or attached to the top of the vagina to correct uterine prolapse or vaginal apical prolapse (apical repair). The Prosima Pelvic Floor Repair Systems are an intra-vaginal approach to POP repair, designed in three configurations to address various pelvic floor repairs: Anterior, Posterior, or Combined.

Placement of surgical mesh through the abdomen (transabdominally) to correct apical prolapse is known as sacral colpopexy, or sacrocolpopexy, and was described using prosthetic slings in 1974. High success rates were reported in the 1980s, and sacral colpopexy has become accepted in the gynecologic community as an effective surgical means to correct vaginal vault prolapse.

**2. Haute Autorité de Santé (HAS) French National Authority for Health. Evaluation of Mesh Implants Installed Through the Vaginal Approach in the Treatment of Genital Prolapse. Department of the Evaluation of Medical and Surgical Procedures.**

At the request of the National College of French Gynecologists and Obstetricians and the French Association of Urology, the French National Authority for Health (HAS) conducted an evaluation of the safety and effectiveness of vaginally implanted mesh for the treatment of genital prolapse.[5] A total of 40 references published in French or English were included in this evaluation (described as: 1 report of a technological evaluation; 1 systemic inspection; 1 descriptive survey of equipment monitoring; 2 open, randomized studies; 1 nonrandom, comparative study; and 34 case studies). The bibliography was not provided in this document.

The HAS critical analysis of the publications found that, in general, studies had non- or under-described inclusion criteria, insufficient staff workers, median follow-up that did not exceed two years, outcome criteria that were poorly described or not described at all, and a lack of consistency in the means of evaluation. In most cases, assessments of efficacy and safety were confounded by "associated" procedures (e.g., concomitant surgery for incontinence or second type of prolapse). The types of implants used in these studies (intended use, whether absorbable, method of implant, precut or uncut) were so variable that nearly every study used a

[5] HAS French National Authority for Health —Evaluation of Mesh Implants Installed Through the Vaginal Approach in the Treatment of Genital Prolapse (translated, French to English) November 2006.

unique implant. Anatomical success rates varied from 46%-100%, depending on the type of prolapse, type of implant, definition of "success," and length of follow-up. Functional success based on symptom improvement was not quantifiable due to variability of symptoms measured across studies and use of non-validated questionnaires or scales.

The documentation of complications was very heterogeneous across studies. A 2005 study conducted in France (referred to as a "materiovigilance study") identified erosions, cellulitis, and abscess as the main complications observed following mesh implantation for urinary incontinence and/or vaginal prolapse. The overall estimated frequency for these complications was 8%, with a duration of follow-up of 10 months and rate of re-operation of 92%. The frequency appeared to be higher in cases of prolapse compared with cases of urinary incontinence. Other studies reported erosion rates of 0% to 24.5%, depending on type of implant used and type of prolapse treated. Two studies reported patient deaths, but did not evaluate whether the deaths were treatment-related. Other complications reported included pulmonary embolism, hemorrhage, wound dehiscence, rectal or bladder injury, rejection of the implant, hematoma, urinary tract infections, surgical wound infections, pain, dyspareunia, de novo urge or stress urinary incontinence (SUI), and de novo prolapse. Frequencies varied among studies. The report stated that some safety studies did not mention severe infections (presumably whether they occurred or not) and these studies also did not perform frequency analysis of complications. No attempt was made to associate complications with the primary surgical endpoint or concomitant procedures. The report acknowledged that some complications could be attributable to pelvic surgery in general.

These findings generated the following comments by experts retained by HAS:

- Preoperative evaluations and duration of follow-up were insufficient;
- Controlled studies were performed only for absorbable, synthetic meshes, which were associated with high recurrence rates;
- The impact on quality of life of complications such as dyspareunia, pain, retractions, erosions, granulomas and infections was not assessed;
- Given the risks of infection, aseptic surgical conditions are required;
- **Only mesh materials validated by clinical trials should be used**;
- Adverse events should be fully reported. (Emphasis added.)

The experts concluded that prospective studies should be performed, including the following elements:

- Pre- and postoperative evaluations using POP-Q classification for anatomical outcome and validated questionnaires for functional outcomes;
- Medium and long-term follow-up (5 to 10 years);
- Exhaustive documentation of adverse events, including elements that may influence the frequency of erosion;
- Evaluation of the management of erosions and retractions.

The overall conclusion of this report was that the available data in the literature at the time this report was written did not allow an effective evaluation of the anatomical and functional

viability of transvaginally placed implants for the treatment of genital prolapse. Serious complications were identified but their frequency was not able to be determined. **Therefore, the French National Authority for Health concluded that the use of mesh implants for transvaginal correction of genital prolapse remained a matter of clinical research.** It is important to note that the date of this conclusion was November 2006, the same month in which Ethicon submitted the Prosima 510(k) to FDA, without clinical data, to obtain clearance to market this device. (Emphasis added.)

### 3. United States Food and Drug Administration (FDA) Literature and MAUDE Database Review

Similarly to the impetus for the HAS evaluation of the safety and effectiveness of vaginally implanted mesh discussed above, by 2008 FDA was aware of potential safety issues with urogynecologic surgical mesh products because of information received through multiple sources. These sources included (1) concerns raised by the clinical community and citizens, (2) the published literature, and (3) postmarket surveillance of the publicly available MAUDE database for medical device reports (MDRs). In 2008, the MAUDE database showed that more than 1,000 MDRs had been received from 2005-2007. These were reports of complications from nine surgical mesh manufacturers of surgical mesh devices used to repair pelvic organ prolapse (POP) and stress urinary incontinence (SUI). A subsequent review of the MAUDE database covering the 2008-2010 timeframe presented POP and SUI complications separately and identified a total of 2,874 MDRs for urogynecologic surgical mesh, of which 1,503 were associated with POP repairs; notably, these MDRs were additional to the 1,000 identified previously in the 2008 MAUDE database search for the years 2005-2007. From 2008 to 2010, there were seven (7) reports of death. Two of the deaths were related to organ perforation and hematoma after surgery, and two were the result of pulmonary embolism. Two deaths followed heart attack/cardiac arrest, and one was related to vessel injury and uncontrollable bleeding.[6]

FDA subsequently undertook a systematic review of the scientific and medical literature from 1996 – 2011 for repair of POP with surgical mesh, identifying 22 reports from randomized controlled trials (RCTs), 38 observational studies, and an additional 15 systematic or meta-analyses. "The majority of the studies evaluated anterior prolapse repair, followed by posterior and apical vaginal repair. The duration of follow-up ranged from perioperative (i.e., intraoperative to 48 hours post-operative) to 60 months. Most studies reported adverse events and outcomes of perioperative period to 12 months postoperative. Only five studies reported a follow-up period beyond 12 months."[7]

"The FDA review identified a number of limitations with the existing literature: (1) results reflect both primary and repeat prolapse repairs; (2) most studies involve concomitant surgical procedures; (3) adverse event reporting is inconsistent; (4) inclusion/exclusion criteria are incompletely documented; (5) the majority of randomized clinical trials are not evaluator-blinded or adequately powered; and (6) few studies extend beyond two years."[8]

"In addition, the literature on POP repair largely represents studies in which the primary

[6] Surgical Mesh for Treatment of Women with Pelvic Organ Prolapse and Stress Urinary Incontinence: FDA Executive Summary. Obstetrics & Gynecology Devices Advisory Committee Meeting, September 8-9, 2011.
[7] *Id.*
[8] *Id.*

endpoint was ideal anatomic support, defined as prolapse Stage 0 or 1 (i.e., the lowest point of prolapse is more than 1 cm proximal to the vaginal opening). This outcome is not based on a correlation with symptomatology and is not necessary for most women to achieve symptomatic relief." [9] "The review showed that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair."[10]

The literature review also revealed the following:

- "Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair.
- Mesh placed abdominally for POP repair appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.
- There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh.
- While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh, this anatomic benefit may not result in better symptomatic results."[11]
- "Erosion of mesh through the vagina is the *most common and consistently reported mesh-related complication* from transvaginal POP surgeries using mesh. Mesh erosion can require multiple surgeries to repair and can be debilitating for some women. In some cases, even multiple surgeries will not resolve the complication.
- *Mesh contraction* (shrinkage) is a *previously unidentified risk* of transvaginal POP repair with mesh that has been reported in the published scientific literature"[12] and in the MAUDE database since the 2008 MAUDE database review. "Reports in the literature associate mesh contraction with vaginal shortening, vaginal tightening and vaginal pain.
- Both mesh erosion and mesh contraction may lead to severe pelvic pain, painful sexual intercourse or an inability to engage in sexual intercourse. Also, men may experience irritation and pain to the penis during sexual intercourse when the mesh is exposed in mesh erosion."[13]
- "The complications associated with the use of surgical mesh for POP repair have not been linked to a single brand of mesh."[14]

### 4. Randomized, Controlled Clinical Trials Comparing Pelvic Organ Prolapse Repair With and Without Mesh

Similarly, my independent assessment of the literature on POP repair shows the majority of studies have been uncontrolled trials, retrospective studies, observational studies, underpowered studies, case series, or studies with incomplete/preliminary findings such as presented at clinical conferences. Furthermore, the primary outcome measure was nearly

[9] *Id.*
[10] FDA *Safety Communication*: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse, Issued July 13, 2011.
[11] *Id.*
[12] *Id.*
[13] *Id.*
[14] *Id.*

always based on anatomical (objective) cure rate or recurrence rate, and often patient-reported outcomes of quality-of-life data were either underreported or not reported. Few trials attempted to blind either patients or evaluators. Another weakness is the absence of long-term follow-up studies. Mesh materials and surgical techniques have also changed over the decades of mesh use, and, therefore, outcomes reported in the earlier literature may not be relevant for later products.

However, reports of 10 prospective, randomized, controlled clinical trials of POP surgery with mesh versus without mesh were reviewed. Notably, two separate publications reporting 3-month and 1-year follow-up, respectively, are discussed for one of these trials. Articles summarized were published between 2008 and 2012. Seven of the studies enrolled patients with anterior prolapse, and three enrolled patients that required surgery for either anterior or posterior prolapse or both. The synthetic meshes used in these trials were all non-absorbable synthetic polypropylene; one study also evaluated vaginal paravaginal repair using porcine dermis graft as a separate study group.

Summaries of prospective, randomized, controlled clinical trials of POP surgery with mesh versus without mesh are attached as Exhibit 5 and incorporated as if set forth fully herein.

### 5. Conclusions of Above Literature Review for POP Repair

The authors of the prospective clinical trials discussed above, comparing no-mesh versus mesh-supported surgery for POP, were in general agreement that the use of synthetic mesh results in superior short-term anatomic outcomes with a reduced failure rate, although Sokol et al.[15] found no statistically significant difference between mesh and no-mesh groups with respect to overall recurrence or recurrence by compartment (anterior or posterior) at one year after POP repair. Importantly, the use of mesh did not result in any advantage over traditional repairs in functional outcomes that measure quality of life (prolapse symptoms, pelvic pain, urinary function, sexual function). When these have been reported, as they have been more comprehensively in later publications, there is little difference in functional outcomes between surgical procedures using mesh and those without mesh, but the use of mesh is associated with additional complications, particularly mesh erosion. Most studies have focused on the use of mesh implants for anterior repair and "[t]here are insufficient data on the use of mesh for the posterior or apical compartments." [16] Furthermore, most published reports of clinical trials have only included a short-term follow-up. Long-term safety and efficacy studies of the use of mesh in POP beyond 4 to 5 years have not been published, and the 4- to 5-year data are minimal. Of the prospective, randomized, controlled clinical trials summarized herein, the longest follow-up was three years (Nieminen et al., 2010), and this study showed little difference in symptom relief, while mesh exposure, a risk that does not exist for native tissue repairs, occurred in 19% of patients implanted with mesh in this study. **Longer follow-up times and more robust data are needed to determine long-term safety and efficacy of products that are intended as permanent implants. Additional studies are needed to assess the risk/benefit of the use of mesh in the correction of POP.** (Emphasis added.)

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[15] Sokol AI et al. One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012;206:86.e1-9.

[16] Committee Opinion Number 513, Committee on Gynecologic Practice, The American College of Obstetricians and Gynecologists and American Urogynecologic Society, December 2011.

### 6. Committee Opinion of ACOG and AUGS Regarding Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse

In December 2011 the American College of Obstetricians and Gynecologists (ACOG) and the American Urogynecologic Society (AUGS) issued a joint opinion on the vaginal placement of synthetic mesh for pelvic organ prolapse repair, based on a review of existing outcome data, including both effectiveness and complications. The 2011 joint opinion was reaffirmed in 2015.[17] The purpose of the jointly issued opinion was "to provide background information on the use of vaginally placed mesh for the treatment of POP and offer recommendations for practice. This report does not address the subject of synthetic mesh used for abdominal or minimally invasive sacrocolpopexy…"[18]

The Committee Opinion reaffirmed that even in 2015, available data were limited. Existing data show "there seems to be a small but significant group of patients who experience permanent and life-altering sequelae, including pain and dyspareunia, from the use of vaginal mesh."[19] The joint ACOG and AUGS report notes that the first surgical mesh indicated for repair of POP and many subsequent mesh products for the same indication were marketed without clinical data. "Mesh kits for repair of POP were first marketed to urologists and gynecologists as a way to improve success rates for POP repairs with native tissue, but without well-designed trials to establish the safety and efficacy of these devices." [20] Among ACOG's and AUGS' conclusions and recommendations of particular relevance to this expert report are the following:

- Vaginal mesh placement for repair of pelvic organ prolapse should be reserved for high-risk individuals in whom the benefit may justify the risk.
- Surgeons implanting vaginal mesh should be experienced with reconstructive surgical procedures, have a thorough understanding of pelvic anatomy, and undergo device-specific traning.
- New products should not be assumed to have equal or improved safety and efficacy compared with existing mesh devices unless clinical long-term data are available.
- Rigorous randomized clinical trials with long-term follow-up to compare the effectiveness of synthetic mesh and native tissue repair are the appropriate standard.
- Informed consent for vaginal mesh placement should be obtained only after a review and discussion of the risks, benefits, and alternatives for POP repair with the patient. [21]

## B. PRODUCT DEVELOPMENT HISTORY: ETHICON'S SURGICAL AND VAGINAL MESH PRODUCTS

### 1. Methodology Used and Construction of Product Development History

To review and evaluate the overall product development history of Ethicon's surgical mesh products leading to the marketing of mesh kits for pelvic organ prolapse repair, a simple search of FDA's searchable 510(k) database was conducted for the following terms:

[17] Committee Opinion Number 513, Committee on Gynecologic Practice, The American College of Obstetricians and Gynecologists and American Urogynecologic Society, December 2011, Reaffirmed 2015.
[18] *Id.*
[19] *Id.*
[20] *Id.*
[21] *Id.*

- Ethicon
- Surgical Mesh
- Prolift
- Prolift+M
- Prosima
- Johnson & Johnson (J&J)

The J&J simple search was further refined using an "advanced search" for the following parameters:

- J&J, surgical mesh; 1 Jan 1998 to 1 June 2012
- Ethicon, surgical mesh; 1 Jan 1998 to 1 June 2012

The result of these searches is presented in tabular format in Exhibit 4 to this Report, which provides a hierarchic representation of the product development and predicate history that eventuated in the marketing of the GYNECARE PROSIMA pelvic floor repair systems. For each product presented, including PROSIMA, information provided includes the indications for use for which the product was marketed, the date the device was first eligible for marketing, and predicate information.

Additionally, I reviewed documentation from Ethicon's files relevant to the product development history of the POP repair mesh kits and reviewed deposition testimony in which the development process for these products was discussed. Key information pertinent to an understanding of the development of the PROSIMA is discussed following.

### 2. Overview: Product Development History of Ethicon's Surgical and Vaginal Mesh Products

PROLENE nonabsorbable polypropylene suture, the first of Ethicon's surgical mesh product line, was initially regulated as a drug and approved by NDA 16374 prior to the enactment of the Medical Device Amendments (MDA) on 28 May 1976. Following passage of the MDA, devices that had been regulated previously as new drugs and approved under New Drug Applications (NDAs) were officially given device status as "transitional devices." A Premarket Approval application (PMA) number with "N" before the application number (which is the original NDA number) denotes a transitional device; the PMA Number for PROLENE is PMA N16374. (The original approval could not be located through online search efforts that included a search of the FDA PMA database, a general search of CDRH, a search of "drugs @ FDA" for approved drug products, and a "Google" search. However, a listing of the supplements to this PMA was found, with a December 31, 1980, decision date for Supplement 001.)

Reclassification under classification regulation 21 CFR 878.5010 as a polypropylene nonabsorbable surgical suture class II device, for use in general soft tissue approximation and/or ligation, including use in cardiovascular, ophthalmic and neurological procedures, was published in the Federal Register on May 31, 1991 (Volume 56, No. 105, Pages 24684-24685). This product is regulated as a General and Plastic Surgery Device: 21 CFR Part 878, Subpart E, Surgical Devices, Nonabsorbable Polypropylene Surgical Suture.

Also in 1991, PROLENE Polypropylene Mesh Plug W/onlay patch was cleared (510(k) number K915774) under classification regulation 21 CFR 878.3300: surgical mesh defined as metallic or

polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples are for hernia repair, acetabular and cement restrictor mesh used during orthopedic surgery. This product also is regulated as a General and Plastic Surgery Device: 21 CFR Part 878, Subpart D, Prosthetic Devices, Surgical Mesh. All the subsequently discussed products in this review were 510(k)-cleared under the classification regulation 21 CFR 878.3300.

The first of 12 Ethicon 510(k)s (that could be identified from the 510(k) searchable database) for the repair of hernia defects was submitted to FDA in 1996 and was a modification of the PROLENE Polypropylene nonabsorbable synthetic surgical mesh. According to the 510(k) Summary of Safety and Effectiveness, the modified device has the same technological characteristics as the predicate device (i.e., no change in chemistry, material or composition), but **differs from the predicate device in the additional sizes supplied and a precut key hole shape provided as a convenience to the surgeon.**[22] The intended use of this Modified PROLENE mesh was specified as "for the repair of hernia and other fascial deficiencies that require the addition of a reinforcing or bridging material, to obtain the desired surgical results. Modified PROLENE mesh has the same intended use as the preamendment predicate device PROLENE mesh."[23] In 2000, PROLENE Soft Polypropylene Mesh, which is knitted by a process which interlinks each fiber junction, **provides for elasticity in both directions** and is 50% more flexible than PROLENE, according to the description in the 510(k) Summary of Safety and Effectiveness,[24] was granted 510(k)-clearance (510(k) number K001122) based on substantial equivalence to Ethicon's PROLENE ((Polypropylene) and MERSILENE Meshes (Ethicon polyester mesh, also a preamendment device). All three of these products, i.e., PROLENE Soft (Polypropylene) Mesh, PROLENE (Polypropylene) Mesh and Mersilene Mesh, served as the predicates for the clearance to market in January 2002 of GYNEMESH PROLENE Soft (Polypropylene) Mesh for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in **vaginal wall prolapse** where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect. (Emphasis added.) GYNEMESH was the first polypropylene mesh support material for female pelvic floor repair to be cleared for marketing.

The first of six 510(k)s for GYNECARE Tension-free Vaginal Tape (TVT) System and its various modifications was granted 510(k)-clearance in 1998 (510(k) number K974098). This product is a pubourethral sling for the treatment of stress urinary incontinence (SUI) resulting from urethral hypermobility and/or intrinsic sphincter deficiency. The TVT device is composed of PROLENE polypropylene mesh (tape), and the mesh is covered with a polyethylene sheath with a slit in the middle.[25]

### 3. Product Development History: GYNECARE PROSIMA® Pelvic Floor Repair Systems

#### *3.1 GYNEMESH PROLENE Soft (Polypropylene) Mesh*

[22] FDA 510(k) Releasable Database: K962530 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K962530.pd.
[23] *Id.*
[24] FDA 510(k) Releasable Database: K001122 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K001122.pdf.
[25] FDA 510(k) Searchable Database: K974098 Summary of Safety and Effectiveness - http://www.accessdata.fda.gov/cdrh_docs/pdf/K974098.pdf.

Gynemesh Prolene Soft Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair is constructed of knitted filaments of extruded polypropylene identical in composition to that used in Ethicon's PROLENE Polypropylene Suture, Nonabsorbable Surgical Sutures, U.S.P. As described in the 510(k) Summary of Safety and Effectiveness for the GYNEMESH PROLENE Soft (Polypropylene) Mesh, "the mesh affords excellent strength, durability and surgical adaptability, with sufficient porosity for necessary tissue ingrowth....The mesh is constructed of reduced diameter monofilament fibers, knitted into a unique design that results in a mesh that is approximately 50 percent more flexible than standard PROLENE Mesh." When the same material has been used as a suture, it has been reported to be non-reactive and to retain its strength indefinitely in clinical use. This mesh is knitted by a process that interlinks each fiber junction and provides for elasticity in both directions, permitting the mesh to be cut into any desired shape or size without unraveling. Purportedly, "[t]he bi-directional elastic property allows adaption [sic] to various stresses encountered in the body."[26] FDA received Ethicon's 510(k) premarket notification (510(k) number K013718) on November 8, 2001, and cleared the GYNEMESH PROLENE Soft (Polypropylene) Nonabsorbable Synthetic Surgical Mesh for Pelvic Floor Repair for marketing on January 8, 2002, for the following Indications for Use: Tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor in vaginal wall prolapse where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect.[27] Notably, the predicate devices for GYNEMESH PROLENE Soft (Polypropylene) Mesh, discussed above, were 510(k)-cleared for hernia repair and repair of other fascial deficiencies, as shown in Table 1.2, Exhibit 4.

GYNEMESH PROLENE Soft (Polypropylene) Mesh was provided in two sizes. For sacrocolpopexy procedures, there was the GYNECARE GYNEMESH™ PS Non-absorbable PROLENE™ soft mesh extra large (25cm x 25cm) designed for abdominal approaches. For vaginal pelvic organ prolapse procedures, there was the GYNECARE GYNEMESH™ PS non-absorbable PROLENE™ soft mesh (10cm x 15cm) designed for vaginal approaches.[28]

### *3.2 GYNECARE PROSIMA Pelvic Floor Repair Systems*

#### *3.2.1 PROSIMA Predicates and Indications for Use*

Ethicon's GYNEMESH (510(k) number K013718) and the Silimed Vaginal Stent (K974479) served as the predicates for the GYNECARE PROSIMA Pelvic Floor Repair Systems. As set forth in the PROSIMA 510(k) premarket notification, the PROSIMA Systems were "indicated for tissue reinforcement and long-lasting stabilization of fascial structures of the pelvic floor, either as mechanical support or bridging material for the fascial defect." Ethicon also intended that "[t]he Systems provide maintenance of the vaginal canal in vaginal wall prolapse, where surgical treatment is intended, reducing the **possibility** of contracture, stenosis, or vaginal canal adhesion, while supporting the position of the Mesh Implants following surgery."[29] This latter sentence was amended at the request of the FDA to: "The Systems provide maintenance of the vaginal canal during the period of healing following surgical repair of vaginal wall prolapse,

[26] FDA 510(k) Searchable Database: K013718, GYNEMESH PROLENE Soft (Polypropylene) Mesh - http://www.accessdata.fda.gov/cdrh_docs/pdf/K013718.pdf.
[27] Indication for Use Statement: K013718, GYNEMESH PROLENE Soft (Polypropylene) Mesh - http://www.accessdata.fda.gov/cdrh_docs/pdf/K013718.pdf.
[28] Ethicon website for Professional Resources, Gynecare Gynemesh PS: http://www.ethicon360emea.com/products/gynecare-gynemesh-ps.
[29] ETH.MESH.05512227 at 371: 510(k) Number K063562, Section 4, Indications for Use Statement.

reducing the **risk** of contracture, stenosis, or vaginal canal adhesions, while supporting the position of the Mesh Implants."[30] (Emphasis added.) This statement was further revised in the final Indications for Use for which the PROSIMA was cleared for marketing to: "The Systems provide maintenance of the vaginal canal during the period of healing following surgical repair of vaginal wall prolapse, while supporting the position of the Mesh Implants."[31]

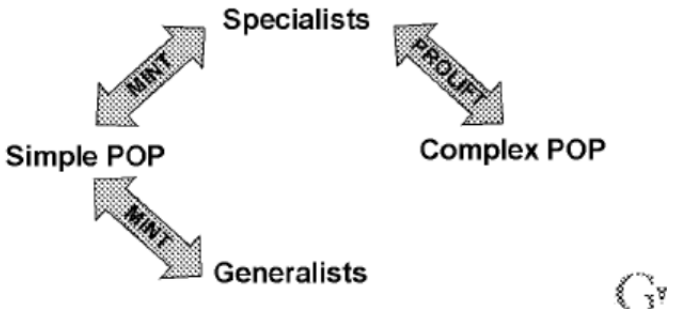
## IV. BASES FOR OPINIONS #1 AND #2

### A. PROSIMA ORIGINAL PRODUCT CONCEPT

In September 2004, Ethicon purchased the intellectual property rights for an anchorless pelvic floor repair device which used a "vaginal support device" or "VSD,"[32] invented by Dr. Marcus Carey (Department of Urogynaecology, Royal Women's Hospital, Melbourne, Vic., Australia).[33] The project initiated to develop this device was named Project Mint, and the resulting product was marketed under the PROSIMA name. The PROSIMA was intended to be a less challenging procedure that would produce better outcomes than native tissue repairs. As one early presentation stated, the "Mint Objective" was as follows:

> "Develop a procedural kit for the surgeon performing pelvic floor repairs entailing a less technically challenging, standardized technique which will improve functional outcomes over traditional native tissue and current flat mesh repairs and will be applicable for most cases of pelvic organ prolapse."[34]

The primary target customer for the device was a less-well trained physician – or "generalist."[35]




The market opportunity was stated as "The generalist needs a durable procedure that is easy to perform."[36] To address that need, the project charter specified that the Project Mint solution would provide a standardized technique with minimal dissection and no graft fixation that a user with normal anatomical knowledge and surgical skills could learn and adopt.[37] The intended value proposition for this device was to improve success, i.e., reduce the incidence of POP

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[30] ETH.MESH.05512227 at 234: Correspondence to FDA, Jan. 25, 2007.
[31] FDA 510(k) Releasable Database: K063562 Summary of Safety and Effectiveness and Indications for Use Statement - http://www.accessdata.fda.gov/cdrh docs/pdf7/K071512.pdf.
[32] *See* WO 2004045457 A1, US 8,201,559 B2 & others: "Method of Surgical Repair of Vagina Damaged By Pelvic Organ Prolapse And Prosthetic Materials And Devices Suitable For Use Therein".
[33] ETH.MESH.00190766 at 776, 799: June 2005 Project Mint Charter Presentation.

[34] ETH.MESH.00190766 at 772: June 2005 Project Mint Charter Presentation.
[35] ETH.MESH.00190766 at 787: *Id*.
[36] ETH.MESH.00190766 at 770: *Id*.
[37] ETH.MESH.00190766 at 774: *Id*.

recurrence, as compared to native tissue repair and minimize complications.[38] Key Opinion Leaders (KOLs) advised Ethicon that clinical data was required as well as an intensive education program for generalists to address the basic science of mesh, surgical up-skilling, and management of complications.[39] Importantly, at the outset of the Project Mint Charter, Ethicon recognized that if the results of the clinical evaluation performed by the inventor (Dr, Marcus Carey) and his development partner, Dr. Mark Slack (Cambridge, United Kingdom) were not favorable, the project should be abandoned or the scope changed.[40]

Early in product development, Dr. Vincent Lucente was presented prototypes of MINT and interviewed to obtain his appraisal and recommendations.[41] Notably, Dr. Lucente is one of Ethicon's leading Key Opinion Leaders and one of the original three surgeons to learn and teach Ethicon's Prolift procedure for mesh repair of pelvic organ prolapse. Dr. Lucente told Ethicon that he had performed a procedure similar to MINT for grade 1 and grade 2 prolapse for some time, placing mesh with no sutures and using a ring pessary to hold the mesh for two weeks after implantation. Based on his personal experience of seeing failures with this technique, he advised Ethicon that an anchorless device would be ineffective for grade 3 or grade 4 prolapse. He also informed Ethicon that he would be suspicious of any data showing efficacy in more severe prolapse patients.

## B. PROSIMA DEVELOPMENT CHALLENGES AND FAILURES

As discussed below, Ethicon failed to achieve the project objectives it established in order to proceed to market with the PROSIMA. Yet Ethicon chose to market this device and, remarkably, for treatment of both grade 2 and grade 3 pelvic organ prolapse. In my professional opinion, Ethicon failed to act as a reasonably prudent medical device manufacturer. Specifically, the company failed to act in accordance both with its own set standard for proceeding to market with this device and also the medical device industry standard of care, which requires that the product benefits outweigh the risks in order to protect the public health.

### 1. Carey, Slack, et al. Clinical Evaluation of PROSIMA Prototype

Disclosure of certain financial interests is the standard or required practice for clinical investigators when submitting clinical study reports for publication in the scientific/medical literature or when submitting safety and efficacy data to support clearance or approval of medical devices for marketing, respectively. Among the main types of financial arrangements that should be disclosed are compensation affected by the outcome of clinical study(ies) and proprietary interest in the tested product. Such financial disclosures are an important aspect of assuring that data accurately reflect clinical performance. Disclosure of Dr. Carey's financial arrangements with Ethicon are pertinent to the following discussions of PROSIMA prototype and PROSIMA clinical evaluations.

According to the Consulting and Assignment Agreement between Dr. Carey and Ethicon, Ethicon initially paid Dr. Carey $500,000 for the intellectual property defining the PROSIMA. Upon marketing of the product, Ethicon would pay another $400,000. Ethicon also agreed to

[38] ETH.MESH.00190766 at 774-775: *Id.*
[39] ETH.MESH.00190766 at 790: *Id.*
[40] ETH.MESH.00190766 at 795, 804: *Id.*
[41] ETH.MESH.06900544: VOC MINT – 4/19/05 – Vincent Lucente, MD, Personal interview with Laura Angelini, Cheryl Bogardus and Vincent Lucente, MD, Orlando, FL.

pay Carey $100,000 upon publication of clinical study results, based on clinical methodology covered under the Patent Rights, in an internationally recognized, peer-reviewed urogynecology, urology, or gynecology journal. In addition, Ethicon agreed to pay Dr. Carey royalties based on sales of the Prosima once marketed.[42]

The initial clinical data for Dr. Carey's device were collected in a prospective, observational study,[43] the results of which were reported in *BJOG: An International Journal of Obstetrics & Gynaecology* in 2008, after having been accepted for publication in October 2007. The reported study was performed with the aim of describing the new surgical procedure and reporting the surgical results. It was conducted principally by Dr. Carey, who contributed 84 cases; 11 cases were contributed by Dr. Slack at the Cambridge, UK, study site, for a total of 95 women who were treated between June 2004 and February 2005. All eligible women with ICS POP-Q stage 2 or more prolapse of the anterior compartment, the posterior compartment, or both were included in the study. Sixty-three women (66%) underwent a repair of both compartments, 26 (27%) underwent a posterior vaginal repair only, and 6 (6%) underwent an anterior vaginal repair only. Gynemesh PS mesh was used for all surgeries. At the completion of surgery, an appropriately sized vaginal support device (VSD) was placed into the lumen of the vagina to support both the vaginal tissues and the positioning of the mesh. The first post-surgery review after subjects were discharged home was at 4 weeks to remove the VSD.

At 6 and 12 months, study participants underwent clinical evaluation and completed a VAS (Visual Analogue Scale) detailing their satisfaction with surgery. Subjects also completed a prolapse-specific validated questionnaire (Prolapse Symptom Inventory and quality-of-life questionnaire [PSI-QOL]). Success was defined objectively as ICS POP-Q stage 0 or 1; stage 2 or more prolapse at any site was documented as a failure. Secondary outcomes included subjective success, complications, QOL outcomes and patients' satisfaction.

The authors reported that 85% of the subjects evaluated at 12 months met the objective success criteria, with 80 subjects (84.2%) returning for the 12-month physical examination. Vaginal pressure symptoms were reduced from 90% (84 of 93 subjects) preoperatively to 13% of subjects evaluated (11 of 84) at 12 months. Eighty-four (84) subjects (88.4%) completed QOL questionnaires and VAS for satisfaction with surgery at 12 months. Sexual dysfunction decreased from 58% of sexually active women (47 of 81) preoperatively to 23% of subjects evaluated (18 of 78) at 12 months. The Prolapse Symptom Inventory and quality of life assessments showed a significant improvement.

The authors reported three significant intra-operative complications: one pulmonary embolus, a rectal perforation, and a pelvic hematoma that required transvaginal drainage. Subjects were asked to report their experience with the VSD, and the authors stated it was generally well tolerated. In three instances, it was removed early at the request of the subject, and one spontaneously extruded two weeks after surgery.

Four instances of mesh erosion were reported; two were treated medically, and two required transvaginal excision of the exposed mesh. Four subjects underwent further surgery to manage sexual dysfunction due to a mid-vaginal constriction in three women and a perineal band in one

[42] ETH.MESH.09746846 at 849-851: September 30, 2004, Consulting and Assignment Agreement between Marcus Carey, MD, and Gynecare Worldwide.

[43] Carey M, Slack M, Higgs P, Wynn-Williams M, Cornish A. Vaginal surgery for pelvic organ prolapse using mesh and a vaginal support device. BJOG 2008;115:391-397.

woman.

The authors concluded that the study outcomes are encouraging, but further clinical studies, including comparative studies, are required to establish the role of this surgery. My review of Ethicon documents discussing this study show a number of concerns that call into question the reliability of this study to support the safety and effectiveness of PROSIMA.

First, as discussed above, the 2008 study publication reports an objective success rate of 85%, with 80 of 95 subjects returning for the 12-month follow-up physical examination. Ethicon's December 7, 2006, Meeting Minutes of the CDMA Europe Meeting, Pelvic Floor Platform, note receipt of the draft manuscript for this publication, which reported apparently excellent results, with an 86% objective success rate at 12 months. However, those same minutes document that Dr. Axel Arnaud reported that the results, which were considered very important for the future PROSIMA launch, were disappointing. Specifically, a closer look at the results showed there was a high rate of patients lost to follow-up: only 73 (not 80) of 95 subjects returned for the 12-month review. If results were expressed on an intention-to-treat basis, they would be far less favorable.[44] A month earlier, Dr. David Robinson, Medical Director, Ethicon Women's Health and Urology, had communicated the same concerns about patients lost to follow-up to Dr. Carey, noting "[t]here were 20+ patients that were not reported on. Is that because they had not reached 12 months or there really were that many lost to follow up? If they really are lost to follow up, it seems the intent to treat population's failure rate then would be 30%+."[45] Notwithstanding these data discrepancies, the final publication in the BJOG reported the more favorable data. Thus, it is noteworthy that Dr. Robinson shared "with everyone some good news" at the time he heard from Dr. Carey that the BJOG had agreed to publish Carey's study but that it would require a major re-write. Dr. Robinson, reflecting on the internal team's concerns about the large number of patients lost to follow-up and that Dr. Carey had submitted the draft manuscript without Ethicon's review, remarked, "This seems the best of both worlds: we get the **chance to revise the data**, Marcus's [sic] wishes to work with the clinical team here in developing the manuscript, and we have the agreement from the journal that they will publish once they are happy with the manuscript."[46] (Emphasis added.) Notably, the published paper includes no disclosure of Dr. Carey's financial interests or Ethicon's involvement.

Numerous documents show that the device/procedure used by Dr. Carey in the observational study was substantially different than the final commercial PROSIMA product.[47] Among the differences was that Dr. Carey included a plication during his anterior and posterior repairs prior to placing the mesh in each compartment,[48, 49] which is not required for the commercial procedure. The colporrhaphy technique used in the study was not well-described.[50] Mesh implant shapes were modified for the commercial product[51] and pre-cut. Gynemesh PS mesh was cut

[44] ETH.MESH.03912703: CDMA Europe Meeting, Pelvic Floor Platform, Meeting Minutes December 7, 2006.
[45] ETH.MESH.03049713: November 2, 2006, Email from David Robinson to Marcus Carey, copied to multiple recipients, RE: Data.
[46] ETH.MESH.06148459: February 5, 2007, Email from David Robinson to multiple recipients RE: Prosima.
[47] ETH.MESH.00455676: January 24, 2007, Email from Allison London Brown to multiple recipients RE: PROSIMA Jan 2007 Update.
[48] ETH.MESH.03048782: September 6, 2005, Email from Kimberly Hunsicker to multiple recipients RE: MINT Post market clinical study.
[49] ETH.MESH.03049713: November 2, 2006, Email from David Robinson to Marcus Carey, copied to multiple recipients, RE: Data.
[50] ETH.MESH.03912703: CDMA Europe Meeting, Pelvic Floor Platform, Meeting Minutes December 7, 2006.
[51] ETH.MESH.03048782 at 785: September 6, 2005, Email from Kimberly Hunsicker to multiple recipients RE:

during surgery and soaked in an antibiotic solution before vaginal insertion in Dr. Carey's study. Also for the commercial product/procedure, a balloon was provided pre-attached onto the VSD and designed to replace postsurgical vaginal gauze packing.

A clinical review of the study results with Dr. Carey and Dr. Slack in December 2006 concluded that their study did not meet the full requirements for the PROSIMA launch needs. Consequently, Ethicon determined to initiate its own PROSIMA clinical study in 2Q07 and wait for a 6-month review of the data before final preparations for the PROSIMA launch.[52]

### 2. No Clinical Performance Data Submitted for Marketing Clearance

Just weeks before the CDMA Europe Meeting described above, on November 22, 2006, Ethicon submitted its 510(k) premarket notification to FDA, seeking clearance to market the PROSIMA. Despite having the above Carey data in its possession, Ethicon chose not to provide the data for FDA's consideration but provided the required Truthful and Accuracy Statement, certifying that all data and information submitted were truthful and accurate and that no material fact related to a substantial equivalence decision had been omitted.[53]

Instead of providing the data, Ethicon submitted a poster describing results from one of the two study centers – Carey's center. Ethicon did not disclose that one of the two publications it was submitting was conducted by the inventor who had a large financial interest in the success of the product. Moreover, Ethicon did not disclose that the company had determined that the data from the study were inadequate to support marketing the product. In addition, Ethicon failed to disclose that the study was conducted with a device/procedure that was substantially different, as discussed above, than the proposed device for which it sought clearance to market. In February 2007, just one month after announcing internally its decision to further study the device, Ethicon received clearance to market the PROSIMA. It is important to note that 510(k) clearance is not an independent finding of the safety and effectiveness of the PROSIMA.

In my professional opinion, Ethicon's 510(k) was false and misleading. Ethicon failed to provide the FDA with critical information relevant to a substantial equivalence decision.

### 3. Ethicon-Sponsored PROSIMA Clinical Study

Protocol 300-06-005, titled "A Prospective, Multi-centre Study to Evaluate the Clinical Performance of the GYNECARE PROSIMA Pelvic Floor Repair System as a Procedure for Pelvic Organ Prolapse," was finalized on March 9, 2007 (Final Version 1),[54] following clearance to market the device on February 26, 2007. The primary objective of this prospective cohort study was to evaluate the anatomical success of the PROSIMA in women with symptomatic ICS POP-Q Stage 2 or 3 prolapse requiring surgical correction. "Secondary objectives included the

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MINT Post market clinical study.

[52] ETH.MESH.00455676: January 24, 2007, Email from Allison London Brown to multiple recipients RE: PROSIMA Jan 2007 Update.

[53] ETH.MESH.05512227 at 376: 510(k) Number K063562, Section 6, Truthful and Accurate Statement.

[54] ETH.MESH.07157112: Protocol 300-06-005, Final Version 1, 09 March 2007, Sponsor ETHICON Global Clinical Development & Medical Affairs.

evaluation of subject reported outcomes (PFDI-20, PFIQ-7, PISQ-12, Euro-QOL), acceptability of the Vaginal Support Device (VSD), length of procedure, length of hospital stay, post-operative pain, return to normal activities, and peri- and post-operative complications."[55]

The study was conducted in 11 sites in the United States, United Kingdom, Germany and Australia with approval from the respective Institutional Review Boards or Ethics Committees.[56] First study patient was consented on May 30, 2007, and the last subject completed study Month 12 on September 23, 2008.[57] One hundred and fifty (150) patients were included in the safety analysis set; 12 of these were device run-in subjects and were excluded from the Full Analysis Set (FAS) and Per Protocol Set (PPS). Placement of mesh was abandoned in two patients because of bladder perforation during dissection; these two patients were included in the safety analysis set but excluded from the FAS and PPS.[58]

Upon receipt of the six-month data, Ethicon delayed the launch a second time. An April 11, 2008, PROSIMA Communication and Action Plan document, forwarded by Alex Gorsky, the current CEO of Ethicon, to Sheri McCoy, then Worldwide Chairman, Surgical Care Group, discusses the reasons for the second delay.

> "PROSIMA has demonstrated encouraging clinical results in the 12-month study of the MINT device (prototype of PROSIMA) accepted by the British Journal of O&G in October last year. Despite the repetition of these results in the 6 month observational study, the preliminary data also shows a wider than anticipated variance in the objective success rates across the 11 investigation centres.
>
> As part of our commitment to ensure the PROSIMA enters the market well supported with clinical data and well-trained customers, the decision has been made to postpone the PROSIMA Pre-Market Preparation activities to undertake further analysis of the clinical results. This course of action is made in concert with Clinical Development, Medical Affairs, EWH&U [Ethicon Women's Health and Urology] senior management who have all reviewed the situation…. This action is prudent to ensure that the factors contributing to outcome variance are identified and well understood, with measures taken to incorporate the best surgical technique into the IFU and training protocols."[59]

Also on April 11, 2008, Judith Gauld, Manager in Clinical Development, emailed Dr. Carey to provide him with the project update that was being sent to study investigators in preparation for the April 26, 2008, PROSIMA Investigator Meeting. The update advised that the 6-month study results showed a wider than anticipated variation in objective success across sites. The key purpose of the investigators' meeting would be to discuss these results, particularly the failures, in order to better understand the data and determine the best course of action to ensure consistency across many sites.[60]

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[55] ETH.MESH.04420750 at 754: PROSIMA Final Report 1 Year, 28 October 2009.
[56] Zyczynski, MD, Carey MP, Smith ARB, et al. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:1.e1-1.e8.
[57] ETH.MESH.04420750 at 753: PROSIMA Final Report 1 Year, 28 October 2009.

[58] ETH.MESH.04420750 at 754: PROSIMA Final Report 1 Year, 28 October 2009.
[59] ETH.MESH.04569706: April 11, 2008, Email from Alex Gorsky to Sheri McCoy RE: PROSIMA Communication and Action Plan doc.
[60] ETH.MEH.10386669 at 677: April 11-23, 2008, Email series between Judith Gauld, David Robinson (copied),

In a subsequent email to David Robinson and Jonathan Meek, Worldwide Marketing Director, on April 12, 2008, in follow-up to receipt of suggestions from Dr. Carey pertaining to the investigators' meeting, Ms. Gauld noted, "We did state in the protocol that the study would be considered a success if the failure rate had an upper 95% CI of less than 20% at 12 months. We have already failed that."[61] Efforts suggested by Dr. Carey to imply otherwise by better "framing" the data would be misleading, i.e., Ms. Gauld was "concerned here that this looks like a good bit of spin going on, and due to his commercial interest, this is not going to come over as objective as perhaps it should."[62]

Prior to the investigators' meeting, Ms. Gauld provide Dr. Carey with a breakdown of success rates by centre: overall and treated compartment. The denominators used were numbers of patients actually returning for the 6-month follow-up. No imputations as regards missing data = success or failure had been made. Number of patients enrolled at each site ranged from 6 to 20 (latter, Drs. Carey and Khandwala). Overall success rates were 12.5%, 33.3%, 38.5%, 60.0%, 61.5%, 75%, 87.5%, 93.3% (one patient of 16 had not yet been evaluated), 93.3% (of 20 subjects, only 11 were evaluated, with five noted as having not returned for 6-month follow-up), 95%, and 100% (of 14 subjects, two had withdrawn, one was lost to follow-up, so only 11 were evaluated). Success rates for treated compartment were the same as overall success rates for all but three sites, for which the success rates for the treated compartment were 25% (vs. 12.5% overall), 53.8% (vs. 38.5% overall), and 69.2% (vs. 61.5% overall). Dr. Carey's overall and treated compartment success rates were 95.0% and Dr. Slack's were 75.0%.[63]

Of 137 patients enrolled in this study, 126 had a 6-month follow-up visit. The 6-month study results across all study sites showed the PROSIMA was successful in 93 patients (73.2%) but a failure in 33 patients (26.8%). At the 6-month visit, 30% of patients were stage 0; 43% were stage 1; and 29% were stage 2.[64]

The minutes from the April 26, 2008, investigators' meeting reflect a range of impressions about the PROSIMA, including the following:

- Uncomfortable using PROSIMA for any larger or more than stage 2 prolapse
- Not a real alternative to Prolift
- Not for isolated prolapse of the apex
- Good for stage 2 and 3 prolapse and apical support in stage 3 patients with a uterus
- Appropriate for uncomplicated primary cases
- Mesh too heavy
- Mesh stiff
- More supple mesh preferable
- Arm fiddly and not secure enough
- Concerns about how to teach this, regarding perfect placement
- Standard methodology needed across group for POP-Q measurements

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and Marcus Carey RE: Prosima Investigator Meeting.

[61] ETH.MESH.03162936: April 23, 2008, Email from Judith Gauld to David Robinson and Jonathan Meek RE: Follow-up on US Visit.

[62] ETH.MESH.03162936 at 936-937: *Id.*

[63] ETH.MEH.10386669 at 673: April 11-23, 2008, Email series between Judith Gauld, David Robinson (copied), and Marcus Carey RE: Prosima Investigator Meeting.

[64] ETH.MESH.10387191 at 197: Prosima Investigator Meeting – Minutes, 26th April 2008, London, UK.

- Subtle but longer learning curve
- Good product but a learning curve.[65]

Six of the nine attending investigators were present for Dr. Robinson's discussion focusing on where the PROSIMA fits. They agreed the product was safe and were "[s]upportive to proceed now as long as we have well trained surgeons who have appropriate research experience to produce proper Registry data."[66]

"Bottom line: PROSIMA needs to meet the challenges of being non-complex, safe and effective."[67]

In April 2009 and June 2009, respectively, the results of this Ethicon-sponsored study were presented at the Annual Meeting of the American Urological Association in Chicago and the 34th Annual Meeting of the International Urogynecological Association, Lake Como, Italy. The one-year study results were accepted in August 2010 for publication in the American Journal of Obstetrics & Gynecology.[68] One hundred thirty-six (136) women were reported as having received the planned surgery, and 95.6% returned for the 1-year assessment. Of these, 76.9% were stage 0/1; however, in 86.9% of the cases, the leading vaginal edge was above the hymen. "Pelvic symptoms, quality of life, and sexual function improved significantly from baseline ($P < .05$). Median visual analog scale scores for vaginal support device awareness and discomfort were 2.6 and 1.2, respectively (0 = none; 10 = worst possible)."[69] Among complications reported, mesh exposure occurred in 12 patients (8.0%). Eight of these resolved after partial mesh excision, and four exposures were ongoing at 1 year. De novo urge and stress urinary incontinence symptoms were each reported by 4% of study subjects. The study authors concluded that "[v]aginal support, pelvic symptoms, and sexual function improved at 1 year, compared with baseline, after trocar-free prolapse repair with nonanchored mesh and a vaginal support device."[70] Of particular note, considering the "Bottom line" for the Prosima, the authors reported that "[t]he surgery appeared to be safe and easy to adopt by experienced vaginal surgeons,"[71] i.e., not by the target customer: the generalist.

However, what is clear from a review of the Protocol and Ethicon's internal documents (although unclear from the published paper), the study failed to meet its primary endpoint. That is, the study failed. Specifically, the Ethicon Clinical Study Report documents that "[i]n the primary analysis (PPS), which excluded the 17 patients in whom the VSD remained in place for less than 21 days, the failure rate was 19.5% (95.2% CI 12.6% to 28.1%)…For the FAS with 12 month data, the failure rate was 23.1% (95.2% CI 16.1% to 31.3%)…In both instances, the upper 95.2% exceeded 20%, hence failing to show the true failure rate is below 20%."[72]

Rather than report that the study had failed its primary endpoint, Ethicon created marketing

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[65] ETH.MESH.10387191 at 194-197: *Id.*
[66] ETH.MESH.10387191 at 198: *Id.*
[67] ETH.MESH.10387191 at 192: *Id.*
[68] ETH.MESH.05169260: Halina M. Zyczynski, MD, Marcus P. Carey, MD, Anthony R.B. Smith, MD, Judi M. Gauld, BSc (Hons), David Robinson, MD, Vanja Sikirica, PharmD, MPH, Christl Reisenauer, MD, Mark Slack, MD, for the Prosima Study Investigators. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:1.e1-1.e8.
[69] *Id.*
[70] *Id.*
[71] ETH.MESH.05169260 at 266: *Id.*
[72] ETH.MESH.04420750 at 760: PROSIMA Final Report 1 Year, 28 October 2009.

designed at undermining the POP-Q as a measure of success and promoted the "functional outcomes." For example, in an "interview" with Dr. Carey (essentially a marketing piece) he downplayed the significance of the POP-Q, indicating it is outdated.[73] Even if this were true, it does not alter the fact that the study used POP-Q as its predefined primary endpoint. In my professional opinion, it was misleading for Ethicon to use this study in its marketing materials without fully disclosing that it was a failed study. Bryan Lisa, EWH&U Associate Director, Regulatory Affairs, corroborates my opinion in correspondence regarding PROSIMA claims. Notably, Mr. Lisa advised Dr. Kirkemo and others in a discussion about making claims for secondary endpoint measures as follows: "There should be disclosures on these pieces using secondary endpoint measures, including a) indication that the primary endpoint did not meet success criteria and b) second endpoint calculation was retrospective.[74]

In addition to burying the primary endpoint, Ethicon attempted to exaggerate its reporting of the functional endpoint. In a November 11, 2009, e-mail Dr. Piet Hinoul, at the time Medical Affairs Director for Europe, Middle East and Africa, wrote about his concerns of overstating the PROSIMA data:

> "Dear Tom, I believe you have been made aware of Judi Gauld's concerns about overstating our success rates for Prosima by quoting the 93.7 percent success rates in the treated site at the level of the hymen."[75]

He expressed his concerns that physicians would not trust the data.

> "[H]er concern that surgeons will question our trustworthiness when they see the full data in the manuscript is indeed founded…I feel that sticking to one of the predefined outcome measures would be more appropriate and less misleading. I'd quote that 88.3 percent of the patients were above the level (not at) of the hymen in the treated compartment. This is still a very good result and will strike the surgeons as believable. Quoting a 94 percent success may lead the surgeons to have unrealistic expectations of the product (leading to its inappropriate use of it in severe stages, or disappointment by their own results)."

While it appears Dr. Hinoul is attempting to do what a reasonably prudent manufacturer would do, I remain concerned that he is defaulting to something that is "less misleading." A reasonably prudent manufacturer would report the data using the predefined endpoints from a study, not search for the least misleading yet favorable result. In response to Dr. Hinoul's frank discussions, Harel Gadot, Group Marketing Director Worldwide, asks that the conversation cease on e-mail. "All, I would like to ask all of us to stop communicating this over the mail."[76]

Considering the above discussion, it is remarkable that the following statement appears at the conclusion of the one-year clinical outcomes publication: "Ethicon Inc. has no independent knowledge concerning the information contained in this article, and findings and conclusions

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[73] ETH.MESH.13758789 at 794-795: GYNECARE PROSIMA Pelvic Floor Repair System – An Expert Interview with Dr. Marcus P Carey, the Inventor of the GYNCEARE PROSIMA System.
[74] ETH.MESH.00573719: November 23, 2009, Email series among multiple staff RE: CDMA call – Prosima Claims.
[75] ETH.MESH.10416655: November 11, 2009, Email series initiated by Piet Hinoul to Tom Affeld, copied to multiple recipients, with response from Harel Gadot RE: Reporting Prosima Success.
[76] *Id.*

expressed are those reached independently by the authors."[77] Moreover, the publication contains no disclosure of Dr. Carey's financial interests in the PROSIMA.

A two-year follow-up of this study was later published.[78] One hundred and ten (110) women of the original 136 study participants agreed to the extended follow-up. Reasons for not re-consenting included the following: previously withdrawn (5); unable to contact (7); refused to return (7); and logistical reasons (7). The median length of extended follow-up was 29 months (range 24-34 months). The primary anatomic success, defined as POP-Q 0-1, was 69.1%. In 84.5% of cases, the leading vaginal edge was above the hymen. Mesh exposure rate was 9.1%. Five percent reported stress urinary incontinence and 3.3% required further prolapse surgery.[79]

### 4. Carey Randomized Controlled Trial: Mesh versus Colporrhaphy

As early as 2005, Dr. Carey and Ethicon were engaged in developing a MINT post-market clinical study. The proposed study design was a randomized controlled non-inferiority trial comparing MINT to traditional colporrhaphy. Rather presciently, in a series of e-mails in September 2005, Dr. Martin Weisberg advised that it would make no sense to market a device that was no more efficacious than native tissue repair, especially if such a device carried increased risks of permanent mesh implantation. He wrote:

> "From what I understand this study proposes to demonstrate 'the non inferiority of anterior MINT, posterior MINT and combined anterior/posterior MINT versus anterior colporrhaphy, posterior colporrhaphy and a combined anterior/posterior colporrhaphy.' Have we discussed this with marketing? Why would we want to introduce a synthetic graft product that does no better than a native tissue repair???"[80]

> "Why would anyone spend any money on a device, and take what they consider a risk of using a graft when they could get the same results for free with native tissue? If we are not confident that this will be better than what our marketing has been claiming is inadequate (native repair) why bother pursuing? If we are confident that we will be able to claim superiority, then we should go for it."[81]

His sentiments were echoed by the marketing team as well. In a September 6, 2005, e-mail, Allison London Brown, Group Product Director, wrote: "[I] would in general agree with Marty's comment on superiority. We need to show that we are providing some type of benefit on the new products we launch, otherwise what is the value to the customer."[82]

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[77] ETH.MESH.05169260 at 267: Halina M. Zyczynski, MD, Marcus P. Carey, MD, Anthony R.B. Smith, MD, Judi M. Gauld, BSc (Hons), David Robinson, MD, Vanja Sikirica, PharmD, MPH, Christl Reisenauer, MD, Mark Slack, MD, for the Prosima Study Investigators. One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:1.e1-1.e8.

[78] ETH.MESH.04420703: Sayer T, Lim J, Gauld JM, Hinoul P, Jones P, Franco N, Van Drie D, Slack M for the Prosima Study Investigators. Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J. 2012 Apr;23(4):487-93. Epub 2011 Dec6.

[79] ETH.MESH.04420703 at 703, 705: *Id.*

[80] ETH.MESH.03048782 at 784-785: August 23 to September 6, 2005, Email series among multiple staff RE: MINT Post market clinical study.

[81] ETH.MESH.03048782 at 783: *Id.*

[82] ETH.MESH.03048782 at 783: *Id.*

In July 2009, Dr. Carey published the results of a randomized controlled trial (RCT), initiated independently but for which he received a study grant from Ethicon, which evaluated whether vaginal surgery with mesh augmentation would reduce the rate of recurrent prolapse at 12 months when compared with traditional colporrhaphy. Complications, symptoms, quality-of-life outcomes, and patient satisfaction with surgery also were evaluated.[83] The study reported on 139 women with POP-Q stage $\geq$ 2 prolapse requiring both anterior and posterior compartment repair. Subjects were randomized to anterior and posterior vaginal repair with mesh augmentation (mesh group, n = 69) or traditional anterior and posterior colporrhaphy (no mesh group, n = 70).

It is noteworthy that the authors report that "[a]ll eligible women who agreed to participate in this study and provided written informed consent were enrolled between February 2003 and August 2005."[84] In particular, this enrollment period overlaps the June 2004 to February 2005 enrollment period of Carey's and Slack's clinical study of the PROSIMA prototype, in which the majority of study participants (63 of 95[66%]) underwent both anterior and posterior repairs. These overlapping enrollment periods for patients requiring repair of both anterior and posterior compartments call into question whether there was enrollment bias or even whether there were patients whose data may have been reported in both studies.

The primary outcome for this RCT was the absence of POP-Q stage $\geq$ 2 prolapse at 12 months. For those subjects who attended the 12-month review, success in the mesh group was 81.0% (51 of 63 subjects) compared with 65.6% (40/61) in the no mesh group and was not significantly different (P-value = 0.07). Both groups reported a high level of satisfaction with surgery and improvements in symptoms and quality-of-life data at 12 months compared to baseline, but there was no significant difference in these outcomes between the two groups. "Vaginal mesh exposure occurred in four women in the mesh group (5.6%). De novo dyspareunia was reported by five of 30 (16.7%) sexually active women in the mesh group and five of 33 (15.2%) in the no mesh group at 12 months."[85] The authors concluded that "vaginal surgery augmented by mesh did not result in significantly less recurrent prolapse than traditional colporrhaphy 12 months following surgery."[86] That is, the PROSIMA prototype failed to show superiority.

As noted above, this was precisely the scenario Dr. Weisberg discussed four years prior to this publication – high-level clinical evidence showing that the Prosima was not superior to native tissue repair and produced more risk. As he stated then, "Why would we want to introduce a synthetic graft product that does no better than a native tissue repair???" Thus, it is also noteworthy that the lead author of the Ethicon-sponsored PROSIMA study advised those co-authors who had suggested final changes to the manuscript for publication, "I did not do an exhaustive search but my review this evening did not find an authoritative paper to support our statement that Prosima outcomes are superior or comparable to colporrhaphy….I really did not feel comfortable stating that we were superior or comparable."[87] In my professional opinion, these was yet other indications that Ethicon should have followed its Risk Assessment Mitigation Strategy and abandoned the Prosima Project.

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[83] ETH.MESH.01187612 at 612, 817: Carey M, Higgs P, Goh J, Lim J, Leong A, Krause H. Cornish A. Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. BJOG. 2009 Sep;116(10):1380-6. Epub 2009 Jul 7.
[84] ETH.MESH.01187612 at 613: *Id*.
[85] ETH.MESH.01187612: *Id*.
[86] *Id*.
[87] ETH.MESH.03129942: December 2, 2009, Email from Halina Zyczynski to multiple recipients RE: Final Prosima paper.

On May 22, 2009, Dr. Carey proposed doing a PROSIMA/colporrhaphy RCT. The response internally at Ethicon noted that upper management would only approve such a study if it could be shown that the study would have a positive impact on sales. "The decision to move to the RCT will distill down to the question posed by senior mgt...'will people change their behaviours as a consequence of the data' followed by 'will it generate sales'."[88] In light of the repeated clinical failures, discussed above, a responsible manufacturer would not tie the need for doing an important study, to establish whether the benefit to risk ratio for PROSIMA was favorable, solely to sales generation.

### 5. Pre-Launch Voice of Customer (VOC) and Internal PROSIMA Concerns

Throughout the development of the Prosima device, Ethicon received feedback, solicited and unsolicited, from its employees, customers and Key Opinion Leaders. As Ethicon acknowledges, such information is crucial for development and maintenance of an effective and safe device. However, this only applies if Ethicon considers and acts appropriately on the advice.

As early as April 23, 2008, Ethicon was informed that one of its most prominent Key Opinion Leaders, Dr, Vincent Lucente, while on a trip as an Ethicon ambassador, "was quite scathing of PROSIMA being a reckless product."[89]

At the Ethicon Women's Health & Urology 2009 Incontinence & Pelvic Floor Summit, held February 6, 2009, in Kissimmee, Florida, Ethicon presented a concept and clinical data review on Prosima to Key Opinion Leaders. In addition, there was a presentation on Prolift about the complications seen with the Prolift device.[90] The Prolift and PROSIMA devices use the same mesh and, in fact, Gynemesh Prolene Soft Mesh was a predicate device for both. In a February 9, 2009, email, Aaron Kirkemo, Associate Medical Director, discussed feedback from the Summit conference. Kirkemo wrote: "I have reviewed my notes of the meeting and a transcript of the synopsis is attached. As you review them, you will find a fairly recurring theme that objections to PROSIMA came up in virtually every venue regardless of what topic was being discussed. The content of the objections were quite consistent no matter who was voicing them. *Most everyone who spoke to me about it felt that the results were not that impressive."[91] The notes also stated: "A second recurring theme was that it did not make sense to use mesh in people with lesser degrees of prolapse given the outcomes." The efficacy results were described as similar to stitch colporrhaphy but with the additional risks of a mesh device, meaning that the risk exceeded the potential benefit. Dr. Kirkemo reported that "[s]everal voiced concerns that it could be 'surgical success rate of stitch repairs with a mesh complication rate higher than Prolift.'" This latter concern was of particular note because, as recognized by the KOLs at the Summit, Ethicon intended to market the device to generalists who did not have the experience with more complicated mesh device procedures. "[T]he surgeons using this may have a mesh handling skill set inferior to the Prolift users."[92]

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[88] ETH.MESH.00591683 at 685, 687: May 22, 2009, to June 5, 2009, Email series among multiple staff RE: Prosima studies moving forward.
[89] ETH.MESH.05009194: April 23, 2008, Email from Rosalyn Harcourt to Jonathan Meek, RE: PROLIFT+ M Registration.
[90] ETH.MESH.00057757: Ethicon WH&U 2009 Incontinence & Pelvic Floor Summit Agenda, February 6, 2009.
[91] ETH.MESH.00281482: February 9, 2009, Email from Aaron Kirkemo to multiple recipients RE: PROSIMA Feedback.
[92] *Id.*

As noted above, years earlier, Martin Weisberg made it clear that if the benefits could not be shown to be better than traditional native tissue repair, the product should not go forward. In fact, Dr. Kirkemo noted that many had concerns that the negative risk-benefit profile of the PROSIMA could endanger the entire pelvic mesh product platform and damage the Company's brand just as the TVT-Secur did.[93]

Further feedback came in a February 9, 2009, email from Andrew Meek, Professional Education Manager, U.S. Team Lead, to Jonathon Meek, Worldwide Marketing Director. "The feelings were very negative towards PROSIMA - the main points of contention are summarized below. [First], the target audience appears to be less skilled generalists. At a time when the scrutiny against mesh is at an all time, [sic] high, why would we want to put a product with questionable data in this groups hands?"[94] And "[t]he potential patient complications for mesh with PFR is [sic] too great to put something like this in the hands of generalists." "The quotes I heard over and over from numerous KOLs were 'Big mistake', 'Don't do it', and 'Give me the VSD and keep Prosima.'"[95] Of particular note, "One KOL said they would no longer work with the company as a matter of principle if we launched Prosima."[96]

As far back as 2006, similar disinterest had been voiced by European Key Opinion Leaders. Specifically, the December 7, 2006, Meeting Minutes of the CDMA Europe Meeting, Pelvic Floor Platform, report "mitigated interest from European KOLs who [were] recently invited to participate to an expert meeting in London."[97] Further, "In light of physicians previous experience, general feeling that this procedure would **not provide enough support** even with the vaginal support device."[98]

In a 2008 PowerPoint about the "Mini-Me" stress urinary incontinence device, a slide entitled, "Watch Out" asked: "Are we willing to go to market with 12 months RCT data from only the inventor's site?" It goes on to cite the Prosima as a cautionary example: "After our Prosima experience demonstrated significant difference between results at inventor's site and other excellent surgeon's sites."[99]

In a later e-mail from September 3, 2009, Piet Hinoul to Jonathan Meek and Harel Gadot and others, Dr. Hinoul summarized "PROSIMA Take Away Messages" from two PROSIMA PMP meetings he had attended. His take away messages included that the proper use of the mesh requires significant skill. "It is also clear to me that this PROSIMA is not the 'mesh for dummies', as I had thought when I first saw its description." Further, "it requires the skill of a pelvic floor surgeon, certainly not 'tier 3.' We cannot make the mistake of putting this into surgeons' hands not used to dissecting the pelvic floor."[100] Dr. Hinoul also advised that the

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[93] *Id*.
[94] ETH.MESH.00548923: February 9, 2009, Email from Andrew Meek to Jonathan Meek, RE: PROSIMA Feedback.
[95] *Id*.
[96] *Id*.
[97] ETH.MESH.03912703: CDMA Europe Meeting, Pelvic Floor Platform, Meeting Minutes, December 7, 2006.
[98] ETH.MESH.03912703 at 704: *Id*.
[99] ETH.MESH.00563685 at Slide 26: PowerPoint titled, "Next Generation Slings – Evaluating Opportunities, Considering Risks."
[100] ETH.MESH.00575818: September 3, 2009, Email form Piet Hinoul to multiple recipients RE: PROSIMA Take Away Messages.

positioning for this device for now must clearly be stage 2.[101]

As discussed previously, the initial goals for PROSIMA included that it should (1) provide a less technically challenging kit; (2) *improve* functional outcomes over traditional native tissue repair; and (3) be applicable for most cases of pelvic organ prolapse.[102] Contrary to these objectives, by the end of 2009 when the PROSIMA was launched to market,[103] numerous Ethicon medical and clinical personnel and Key Opinion Leaders had concluded: (1) the device was "not the mesh for dummies"; (2) did not improve outcomes over native tissue repair, but carried additional risks; and (3) should be limited to only POP-Q grade 2 repairs. In my professional opinion, a reasonably prudent medical device company would not have proceeded to market this device.

Despite these concerns, Dr. Hinoul discussed how important it was to launch Prosima because of impending competition. He reported that "PROSIMA, with the evidence backing it up, is our perfect/timely weapon against both Pinnacle that will be hitting the UK soon and Elevate, which I expect to be starting their aggressive sales techniques soon…As both these products are ready to start hitting Europe, and Pinnacle is already giving us a headache in the U.S., there can be no delay for proceeding with PROSIMA with its current mesh." Regarding "current mesh," Ethicon had already developed the PROLIFT+M which provided a partially absorbable mesh – a potentially better design alternative if Ethicon would include the newer mesh in the PROSIMA. Dr. Hinoul argued against immediately upgrading to the partially absorbable mesh for the PROSIMA even if it were considered safer, apparently because any delay would hurt business.[104] This is particularly concerning given that it is the Medical Affairs Director for Europe, Middle Easet, and Africa, voicing this market-based recommendation.

In or about December 2009, Ethicon launched the Prosima. By April 19, 2010, sales were booming. In an email from Kevin Frost, Product Director for GYNECARE PROSIMA Pelvic Floor Repair Systems to Leslie Fronio, Andrew Meek, and others, the subject is "$1 million!!!!!!!!!!!" He wrote, "We have hit a very significant milestone with the PROSIMA launch, $1 million dollars in sales! This makes PROSIMA one of the fastest launches ever, in the mesh kit market!"[105]

### C. DEFICIENCIES REQUIRING RESOLUTION PRIOR TO PROLIFT CLEARANCE TO MARKET AND IMPLICATIONS FOR PROSIMA

As discussed in more detail in my Prolift Report, which I incorporate herein, on August 24, 2007, Ethicon received a letter signed by David Krause for Mark Melkerson, Director, Division of General, Restorative and Neurological Devices, Office of Device Evaluation, CDRH, requesting Ethicon to address multiple (16) deficiencies in order for the Agency to complete review of Ethicon's Prolift 510(k) submission. These communications are relevant for PROSIMA because, as noted above, PROSIMA used the same mesh as the Prolift device and was for the same intended use. Hence, even though Ethicon had already received clearance to

[101] ETH.MESH.00575818 at 819: *Id.*
[102] ETH.MESH.00190766 at 772 (June 2005 Project Mint Charter Presentation).
[103] December 6, 2009, Executive Summary prepared by Bryan Lisa, Associate Director, Regulatory Affairs, RE: Regulatory Strategy for the Promotion of GYNECARE PROSIMA™ Pelvic Floor Repair Systems for Specific Use – RAXXXX-2009 (no Bates number).
[104] ETH.MESH.00575818 at 819: September 3, 2009, Email form Piet Hinoul to multiple recipients RE: PROSIMA Take Away Messages.
[105] ETH.MESH.00794750: April 19, 2010, Email from Kevin Frost to multiple recipients RE: "1 Million Dollars!!!!!!!!!!

market the PROSIMA, a reasonably prudent medical device manufacturer would have ensured that applicable identified deficiencies were also addressed for the PROSIMA.

In its letter, the FDA asked Ethicon to provide a rationale for substantial equivalence of the Prolift and Prolift+M Systems to the predicate devices, stating that the unique shapes of the meshes in the Prolift Systems are significantly different from previously cleared rectangular meshes and "have the potential to raise new questions of safety and effectiveness given that surgical procedure using the Prolift Systems will not be equivalent to the surgical procedure for placement of the predicate devices."[106] Since Prolift (originally listed as a predicate device for the Prolift+M) was now a candidate device for 510(k) clearance (K071512), the two remaining predicate devices were the ULTRAPRO mesh (K033337) and GYNECARE GYNEMESH PROLENE Soft (polypropylene) Nonabsorbable Synthetic Surgical Mesh (K013718).[107]

Almost half of FDA's listed deficiencies were related to clinical evaluation and use concerns. FDA asked for clarification regarding whether any clinical studies had been conducted with either the Prolift or Prolift+M and requested complete study reports for any study(ies) done.[108] FDA asked for justification of Ethicon's conclusion that clinical evaluation of the meshes was not necessary, citing cautionary remarks in a publication in the 510(k) submission concerning the use of biomaterials in pelvic surgery because of the mesh size and resultant increased biomaterial load. Moreover, FDA advised that a significant number of adverse events had been reported to the Agency both for the TVT device and also the GYNEMESH device. The latter is identical in composition and intended use not only to the Prolift System but also to the PROSIMA Systems. Accordingly, FDA requested discussion concerning how the Prolift System can be used safely and effectively, "taking into account these reported adverse events."[109] All of these concerns also applicable to the PROSIMA and, at a minimum, put Ethicon on notice that it should also address these issues for the PROSIMA. Among the other deficiencies FDA identified with regard to the Prolift were questions related to technological and performance characteristics and labeling issues. Identified labeling concerns were also applicable to PROSIMA labeling.

On September 20, 2007, Ethicon submitted its response (K071512 – S02) to the deficiencies listed in FDA's August 24, 2007, letter.[110] The response was supplemented on October 15, 2007, with K071512 S03.[111]

In response to FDA's inquiry concerning how the Prolift could be used safely and effectively, considering the number of complaints and Medical Device Reports (MDRs) reported to FDA for GYNEMESH, Ethicon compared adverse event rates for GYNEMESH and PROLIFT and concluded that MDR rates (number reported/sales) were comparable for the time period evaluated (2005 through 2007 YTD). Further, Ethicon reported to FDA that "Through Design Validation and cadaver modeling, GYNECARE PROLIFT and GYNECARE PROLIFT+M have been shown to not introduce new issues of safety and efficacy from the predicate, GYNECARE GYNEMESH."[112]

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[106] ETH.MESH.00372330: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[107] ETH.MESH.00748571 at 617: Traditional 510(k) Premarket Notification – PROLIFT+M Pelvic Floor Repair Systems, Substantial Equivalence – Predicate Devices.
[108] ETH.MESH.00372330: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[109] ETH.MESH.00372330 at 331: *Id.*
[110] ETH.MESH.00372336: Email, September 20, 2007, from Bryan Lisa to Jiyoung Dang, FDA, RE: K071512 – S02.
[111] ETH.MESH.00372640: Ethicon's K071512 S03 submission to FDA, 10/15/07.
[112] ETH.MESH.00372341 at 344-345: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.

However, Ethicon did not disclose to FDA that clinical experience with PROLIFT had led Ethicon to a decision to reengineer PROLIFT, which resulted in the development of PROLIFT+M.[113] Specifically, "The Prolift+M® was designed in a response to minimize the mesh load given to the patient and increase the flexibility of the mesh that was being used in the pelvis," with the desire that this would benefit the patient, both from a safety and efficacy standpoint.[114] As discussed above, it appears that Ethicon also considered using the partially absorbable mesh used in Prolift+M for the PROSIMA for similar reasons, but chose not to do so in an effort to proceed without delay to market a "timely weapon" against competitive products.

Ethicon also did not disclose to the FDA that by November 2005, Dr. Jacob Eberhard, a European (Switzerland) surgeon who had done over 70 PROLIFT surgeries, had brought a number of PROLIFT safety issues to the attention of Ethicon, namely, Axel Arnaud, Scientific Director, Gynecare Europe.[115] Nor did Ethicon report to FDA that by November 24, 2006, it was known there were two issues with the PROLIFT from the perspective of some experts, including Professor Jacquetin, who created the PROLIFT product or was the leader of the team that created the product: erosions and shrinkage.[116] At this point, the erosion and shrinkage problems were significant enough that Ethicon was trying to find a way to address them.[117] According to Dr. Robinson's testimony, both the mesh and the surgical technique can be factors leading to erosion.[118] As regards shrinkage, it was believed the responsibility of the mesh was more established and "further to the expert's discussion, it was speculated that Ultrapro could be (not is) a solution for this problem, which is less common but can be more severe than erosion."[119] (Note that the mesh doesn't shrink but the problem is described as shrinkage.[120])

Moreover, Ethicon confirmed to FDA that the following statement, for which Ethicon agreed that sufficient evidence had not been provided, had been removed from the IFU: "The bi-directional elastic property allows adaptation to various stresses encountered in the body."[121] However, this statement remained in the PROSIMA IFU for its entire life-cycle, as discussed further below.

***OPINION #1: <u>Ethicon Obtained Clearance to Market the PROSIMA based on False and Misleading Information and Representations.</u>***

Ethicon's representations to obtain clearance to market the PROSIMA were false and misleading by its failure to disclose important safety and effectiveness information concerning the PROSIMA and, moreover, advising FDA that all necessary risk information was included in the Instructions for Use (IFU). As a consequence of these violations of the standard of care required of a medical device manufacturer, the PROSIMA was cleared for marketing based on information that was materially inaccurate and incomplete. It is my professional opinion, based on my knowledge, training, and experience in medical product development, that PROSIMA

[113] Dr. David Robinson deposition, 3/14/2012, 350:6-10.
[114] Dr. David Robinson deposition, 3/14/2012, 350:22-351:11.
[115] Dr. David Robinson deposition, 3/14/2012, 369:22-371:10; 374:10-18.
[116] Dr. David Robinson deposition, 3/14/2012, 447:10-448:15.
[117] Dr. David Robinson deposition, 3/14/2012, 451:17-24.
[118] Dr. David Robinson deposition, 3/14/2012, 449:20-24.
[119] Dr. David Robinson deposition, 3/14/2012, 450:19-451:16.
[120] Dr. David Robinson deposition, 3/14/2012, 448:22-449:1.
[121] ETH.MESH.00372341 at 351: K071512 S02, submitted to Jiyoung Dang, FDA, 9/20/07.

would not have been cleared to market without clinical evidence demonstrating safety and effectiveness if Ethicon had disclosed the relevant information it possessed, as discussed above, concerning PROSIMA, including the underlying clinical data issues, Ethicon's internal concerns, feedback from key opinion leaders (KOLs), adverse events, and that moderate prolapse (stage 2), for which Ethicon intended the PROSIMA to be used, typically had not been treated with surgical intervention.

***OPINION #2:*** ***The PROSIMA Device Was Never, Including at Launch and Through the Date of Its Market Withdrawal, Supported by Appropriate Studies, Testing and/or Data To Support Safety and Efectivenes for a Permanent Implant; Marketing Should Have Been Abandoned.***

The clinical studies that did exist were fraught with inadequacies, but even so, still revealed the serious safety and effectiveness concerns associated with the product. Internally, Ethicon employees and consultants considered PROSIMA reckless and questioned whether its benefit-risk ratio was favorable. Ethicon had information from key opinion leaders who advised that the risks of the PROSIMA device outweighed the benefits. Ethicon's senior executives were included in discussions and presentation as to the inadequacies and/or failures of the existing studies. Based on the information known or knowable to Ethicon, a reasonably prudent medical device manufacturer, committed to pursuing marketing of the product, would have undertaken pro-actively the appropriate, controlled clinical study(ies) to identify the patient population, if any, for which the potential risks were justified by any potential benefit. Ethicon did not initiate any such study. And at no time did Ethicon share with the public its internal knowledge related to the deficiencies of the PROSIMA clinical data or the feedback form KOLs warning against the marketing of PROSIMA, particularly for use by less skilled generalists, the target customer. Ethicon failed to follow the requirement it created for releasing the PROSIMA onto the market. If Ethicon had followed its own internal requirement related to the safety and performance of the PROSIMA, this device never would have been released to the market. For all medical devices, the internationally accepted standard of care is that a clinical evaluation of the device, including clinical data in the form of clinical studies, medical and scientific literature, and/or clinical experience must demonstrate that a favorable benefit-risk ratio exists for the device. In my professional opinion, evidence did not exist to support a finding by a reasonably prudent medical device manufacturer that the benefits of the PROSIMA outweighed the risks, and marketing of the PROSIMA should have been abandoned.

## V. BASES FOR OPINIONS #3 and #4

### A. PROSIMA PROFESSIONAL LABELING

Based on the "IFU Index and Production Bates Range Chart" provided by Ethicon's counsel, there has been one version of the PROSIMA Instructions for Use (IFU), which was used from launch until the product was discontinued. However, the first use date is shown as 06/18/10. The deficiencies in the Prosima IFU are discussed in detail below.

#### 1. "Bi-directional" Statement

During the review of the proposed labeling for the Ethicon Prolift, submitted in the 510(k) (K071512), FDA advised Ethicon in a letter dated August 24, 2007[122] (and in an email dated August 27, 2007[123]), that: "You have not provided sufficient evidence to support the statement 'the bi-directional elastic property allows adaptation to various stresses encountered in the body.'" Ethicon was requested either to remove the statement from the Instructions for Use or "provide *in vivo* experimental evidence" demonstrating the "mesh has elastic properties that allows adaptation to physiological stresses."[124]

Ethicon reported to FDA in its September 20, 2007, response, that "We agree that sufficient evidence has not been provided to make this statement. We have removed the statement from the [Prolift] IFU."[125] On January 22, 2008, Bryan Lisa, then Project Manager, Regulatory Affairs, Ethicon, again told FDA that the PROLIFT IFU "will be updated to remove the 'bi-directional elasticity' statement..."[126] And once again in Ethicon's response to FDA on February 21, 2008, Mr. Lisa confirmed the "bi-directional" statement had been removed.[127]

Hence, Ethicon admitted in 2007 that it did have evidence to support, specifically the claim related to the mesh "bi-directional elastic property." However, Ethicon knew internally, and from VOC from physicians, that elasticity was a mesh characteristic that was important to reducing complications in women. Despite admitting that deleting this claim was necessary and appropriate, Ethicon failed to make this change to the PROSIMA IFU prior to marketing the device in 2009/2010 and, in fact, never made the change for the PROSIMA IFU up to and through its removal from the market.

#### 2. Clinical and Safety Information to be Included in IFU For Prolift Not Implemented for PROSIMA

In a December 20, 2007, letter to Ethicon concerning the Prolift 510(k), FDA listed a number of remaining deficiencies which Ethicon was required to address in order for FDA to render a substantially equivalent decision for the Prolift device. A number of those deficiencies involved professional and patient labeling issues and, notably, also a request for financial disclosure information for the Trans-Vaginal Mesh (TVM) clinical study of the Prolift prototype mesh. Ethicon received this letter discussing these IFU deficiencies at least two years prior to initial

[122] ETH.MESH.00372330 at 333: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[123] ETH.MESH.00081118: Email, 21 Aug 2007, from Jiyoung Dang to Bryan, Lisa RE: K071512 – AI letter.
[124] ETH.MESH.00372330 at 333: August 24, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512.
[125] ETH.MESH.00356982 at 992: Ethicon's K071512 S02 Submission to FDA, 9/20/07.
[126] ETH.MESH.00372662: 1/22/08 Meeting Minutes (via Teleconference) RE: Discussion of AI Letter (K071512).
[127] ETH.MESH.00372664 at 668: 2/21/08 Response to FDA's 12/20/07 Letter RE: K071512 S04.

marketing of the PROSIMA device; yet, Ethicon did not rectify these same deficiencies in the PROSIMA IFU. There is no justifiable rationale to support that the PROSIMA IFU would be adequate for the safe and effective use of PROSIMA without inclusion of the applicable safety and effectiveness information required to be included in the Prolift IFU.

FDA found that the draft IFU for the Prolift "[did] not adequately address issues of usability and potential adverse events," and labeling revisions were requested based on information from three sources: 1) data reported in the Trans-Vaginal Mesh (TVM) placement clinical evaluations (both European and U.S. cohorts); 2) analysis of adverse events reported to the FDA for the Prolift device; and 3) conclusions from publications specifically addressing Prolift device use.[128] Adverse reactions, contraindications, warnings, physician training, and summaries of the TVM placement clinical evaluations were among the information that were to be revised or added for the Prolift IFU. Ethicon also was instructed that these sections of the IFU should be written in prominent text and placed before the section illustrating the recommended surgical technique. A review of the Prosima IFU reflects that, irregardless of learning the necessity and importance of these revisions to the Prolift IFU, Ethicon chose not to independently address the same deficiencies for the Prosima IFU.

It is important to understand that Ethicon was advised of the context in which these changes to the IFU were required. Specifically, Ethicon was advised that an action team had been formed at FDA to deal with the adverse events associated with pelvic floor repair meshes and, importantly, was told "this IFU information will be enforced for devices of this nature in the future" and "these changes are 'across the board'".[129] Ethicon could have no doubt that the relevant changes would apply to the PROSIMA IFU. It is my professional opinion that a reasonably prudent medical device manufacturer would have implemented those changes, appreciating that adequate labeling is a cornerstone of risk management.

For the Prolift, FDA believed it was important to include a summary of the clinical data from the TVM internal study reports (noted above) in the IFU, due to the serious nature of the Medical Device Reports received by FDA and associated with anterior/posterior vaginal wall repairs using the predicate device: GYNECARE GYNEMESH.[130] Prior to the marketing of the PROSIMA in or about December 2009, Ethicon had available, at a minimum: (1) the Carey investigational data (and the fact that the data showed a less favorable success rate when properly accounting for loss to follow-up); (2) the Carey RCT showing the PROSIMA prototype was not superior to traditional techniques but exhibited a higher complication rate, specifically erosions; and, (3) its own sponsored study data which failed to meet its pre-specified endpoint for success. A summary of these clinical data should have been included in the PROSIMA IFU.

***2.1 Adverse Reactions***

FDA provided Ethicon with a list of adverse events to be included in the Prolift IFU in its December 20, 2007, letter to Ethicon concerning deficiencies in the PROLIFT 510(k) (K071512/01).[131] These included:

- hematoma

[128] ETH.MESH.00372653 at 655: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.
[129] ETH.MESH.00372653 at 655-656: *Id.*
[130] ETH.MESH.00372653: *Id.*
[131] ETH.MESH.00372653 at 655: *Id.*

- urinary incontinence
- urinary retention/obstruction
- void dysfunction
- pain
- infection
- adhesions
- wound dehiscence
- nerve damage
- recurrent prolapse
- contracture
- procedure failure.

As with the Prolift, some of these events were already in the PROSIMA IFU. However, despite knowing in December 2007 that all of these events should be included, Ethicon failed to add the others to the PROSIMA IFU when it was marketed at least two years later. These adverse reactions never appeared in the PROSIMA IFU.

In addition, Ethicon's adverse reactions, warnings and precautions failed to address or misrepresented the actual risks of using the device. For example, by using the phrase that adverse reactions are those "typically associated with surgically implantable materials," Ethicon misled physicians about the known potential severity and seriousness of risk that its studies had demonstrated. Ethicon employees have testified that chronic pain and lifelong complications were known risks at the time Ethicon launched its POP mesh products. Yet Ethicon did not include any language related to the potential for long-term, chronic, irreversible and life-long complications associated with the PROSIMA mesh in the IFU.

My review of the relevant scientific and medical literature, deposition testimony, and internal Ethicon documents shows there were a number of other potentially clinically significant complications that were known or knowable to Ethicon but were missing from the PROSIMA IFU. Medical device labeling should include all adverse or undesirable effects that are expected and foreseeable, including any relevant information that must be conveyed to the patient. Among the additional missing potential complications were the following (presented alphabetically for purposes of this report):

- Abscess
- Cellulitis
- Constipation
- Deep vein thrombosis
- De novo fecal incontinence
- Difficulty standing or walking`
- Foreign body reaction, chronic
- Granuloma
- Hemorrhage
- Implant rejection
- Pain with defecation
- Sepsis
- Seroma/fluid drainage
- Sinus tract formation
- Ureteral injury or obstruction

- Urinary tract infection
- Vaginal discharge
- Vaginal shortening or stenosis

### *2.2 Contraindications*

The "Contraindications" section in the PROSIMA IFU from 2009/2010 stated as follows:

> When GYNECARE GYNEMESH PS mesh is used in infants, children, pregnant women, or women planning future pregnancies, the surgeon should be aware that this product will not stretch significantly as the patient grows.
>
> The GYNECARE PROSIMA System should not be used in the presence of pregnancy or purulent infections or cancers of the vagina, cervix, or uterus.

However, the IFU that Ethicon submitted to FDA in 2007 to resolve 510(k) deficiencies prior to clearance of the Prolift for marketing included the following "Contraindications":

> 1. GYNECARE GYNEMESH PS Mesh should not be used in infants, children, pregnant women, or women planning future pregnancies, as the mesh will not stretch significantly as the patient grows.
> 2. GYNECARE GYNEMESH PS Mesh must always be separated from the abdominal cavity by peritoneum.
> 3. GYNECARE GYNEMESH PS Mesh must not be used following planned intraoperative or accidental opening of the gastrointestinal tract. Use in these cases may result in contamination of the mesh, which may lead to infection that may require removal of the mesh.
> 4. The GYNECARE PROLIFT Systems should not be used in the presence of active or latent infections or cancers of the vagina, cervix, or uterus.

Contraindications #2 and #3 never appeared in the PROSIMA IFU (although Ethicon did add them to the Prolift IFU on October 1, 2009 – before the PROSIMA IFU was distributed to the market). Nor did the contraindications appear in the location and prominence on the IFU required by FDA for the Prolift IFU.

Further, Ethicon had information that certain patient populations were more likely to experience negative outcomes as a result of the use of the Prolift System. Such information should have been included in the contraindications section of the PROSIMA IFU as well.[132] Dr. Hinoul, Ethicon's Medical Affairs designee, testified at the FDA Obstetrics and Gynecology Devices Advisory Committee meeting in September 2011 that certain patient populations were at higher risk for complications from the Prolift System and testified in his deposition that Ethicon was aware of this fact since the time of the Prolift launch.[133] Ethicon failed to include this important

[132] Catherine Beath deposition, 3/26/12, 114:2-115:12

[133] Piet Hinoul deposition 4/6/12, 480:8-480:20; Hinoul FDA Advisory Committee Testimony at pg 145 ("One of the most important questions we need to ask ourselves is also why these adverse events are occurring. And the risk factors for mesh exposures are becoming more and more apparent. Several studies published this year show that hysterectomy, patient age, smoking, diabetes, and surgeon experience predispose patients to mesh exposure. Patient selection and risk factors, appropriately stated in the device's labeling, as well as the surgeon's training, are therefore part of our proposal.")

information, pertinent to the safe and effective use of the device, in the contraindications section of the PROSIMA IFU (where there is no reason to believe the experiences would be different), or anywhere else in the labeling materials.

### *2.3 Performance*

The IFU for PROSIMA also included a "Performance" section which stated as follows:

> Animal studies show that implantation of GYNECARE GYNEMESH PS elicits a minimal to slight inflammatory reaction, which is transient and is followed by the deposition of a thin fibrous layer of tissue which can grow through the interstices of the mesh, thus incorporating the mesh into adjacent tissue. The mesh remains soft and pliable, and normal wound healing is not noticeably impaired. The material is not absorbed, nor is it subject to degradation or weakening by the action of tissue enzymes.[134]

Ethicon had information that the above statement was untrue as it relates to the PROSIMA. Specifically, the minutes of an Ethicon expert meeting on June 2, 2006, show that Ethicon was aware that fibrosis is responsible for complications in mesh usage and that mesh creates a foreign body reaction that is not transient but rather an active process, a "chronic wound" that contributes to mesh contraction.[135] Ethicon was also aware that the "scar plate that forms with in-growth of tissue into the mesh can cause stiffness of the vagina," which was contrary to any statement regarding the mesh remaining soft and pliable post implantation.[136]

### *2.4 Warnings and Precautions*

Serious complications such as those that may result in persistent or significant incapacity or have the potential to substantially disrupt a patient's ability to conduct normal life functions should be described in the Warnings section of the product labeling, in addition to those that may require medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Other clinically significant complications, e.g., those that occur frequently and have implications for patient management or may lead to a potentially serious outcome, also should be included in the Warnings section. As applicable, the description of a complication in the Warnings section also should include actions to be taken to reduce the likelihood or severity of the event and how to monitor for or manage the event.

The Warnings and Precautions in the PROSIMA IFU were incomplete in my professional opinion, in particular, because they failed to convey the frequency, seriousness, and life-altering nature of certain potential complications. Notably, the Warnings and Precautions listed below (or similar wording) should have been included in the PROSIMA IFU.

- patients may require numerous additional surgical procedures to treat complications from the PROSIMA which may not alleviate those complications, may exacerbate those complications and may bring about additional complications;

[134] ETH.MESH.02341398 at 409: Gynecare PROSIMA Instructions for Use (IFU).
[135] ETH.MESH.00870466 at 467: Minutes - Ethicon Expert Meeting, Meshes for Pelvic Floor Repair, June 2, 2006.
[136] ETH.MESH.00081478: PROLIFT+M Pelvic Floor Repair System, Clinical Strategy, February 4, 2008.

- complications have been shown to be higher with mesh placement compared to traditional non-mesh repair;
- while transvaginal repair with mesh may provide anatomic benefit compared to traditional, non-mesh POP repair, it may not provide better symptomatic results;
- complications in many situations are not "unlikely" or "self-resolving," and may be chronic, irreversible and/or permanent;
- patients may experience chronic, permanent and debilitating pain;
- the implantation method was never standardized and is ill-defined, as demonstrated by wide variation in outcomes amongst clinical investigators using the product;
- patients may experience permanent, severe sexual dysfunction, including severe pain with intercourse and inability to ever engage in coitus for the rest of their life;
- patients may experience severe urinary problems, including voiding dysfunction, urinary obstruction, increased urinary tract infections and others;
- the PROSIMA may never be able to be entirely removed, multiple surgeries may be required which may not alleviate the device-related adverse effects and could cause further complications; pelvic pain and other complications may become worse over time even after multiple revision surgeries;
- the safety and effectiveness of this device have not been adequately established;
- the PROSIMA can cause permanent groin and/or leg pain, buttocks pain, weakness, numbness and nerve irritation;
- erosions of the mesh can be severe, incurable and recur repeatedly for the rest of the patient's life;
- as the FDA has stated, complications from this device type are not rare;
- as the FDA has stated, it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair in all patients with POP and it may expose patients to greater risk;
- as the FDA has stated, the literature shows that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair;
- as the FDA has stated, mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair;
- PROSIMA mesh could result in painful and persistent scarring, scar bands and scar plates in and/or near the vagina;
- serious and chronic inflammation could occur with the use of PROSIMA and this complication may not be slight or transient (as stated in the IFU);
- there is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh;
- PROSIMA may cause injury and irritation to a woman's partner during intercourse;
- PROSIMA has not been adequately studied in candidate women to establish safety and effectiveness;
- onset or recurrence of complications associated with PROSIMA could be delayed for years following the date of implant and could then be permanent in nature; and
- Patients with prior pain syndromes are at a heightened risk of mesh failure and resulting complications, including new onset of pain, aggravation of pain, and

resulting permanent, irreversible pain that may continue to get worse over time with or without the presence of the mesh.

### *2.5 Physician Training*

In its December 20, 2007, letter listing deficiencies in the Prolift 510(k), the FDA requested Ethicon to expand the statement in the IFU that recommends training in the use of surgical mesh for pelvic organ prolapse also to include training in the management of complications resulting from such procedures.[137] The statement submitted to FDA in the final proposed labeling prior to 510(k) clearance was the following: "Training on the use of the GYNECARE PROLIFT Pelvic Floor Repair Systems is recommended and available. Contact your company sales representative to arrange for this training. Physicians should have experience in management of complications resulting from procedures using surgical mesh."[138] This last sentence – the one specifically requested by the FDA – was never in the PROSIMA IFU.

This is of particular concern with the PROSIMA device, as Ethicon targeted less-experienced physicians as the primary market for the PROSIMA. In fact, as early as 2005, Ethicon had VOC feedback that "[a]mong generalists, an intensive education program is required to address basic science of mesh, surgical up-skilling and mgmt. of complications."[139] Later Ethicon's Medical Director, Piet Hinoul admitted that the PROSIMA was not for "dummies" as he had originally been led to believe. Ethicon improperly marketed PROSIMA by targeting inexperienced physicians and non-mesh users, failing to warn physicians about complications/risks of the mesh system, failing to properly instruct physicians on management of complications, as well as failing to account for learning curves and bias in the data compiled on the PROSIMA.

## B. PATIENT BROCHURE (PATIENT LABELING)

Patient labeling is defined as any information associated with a device that is targeted to the patient (or lay caregiver).[140] The two general categories of information in patient labeling are risk/benefit information and instructions for use. For implants, such as the PROSIMA, patient labeling generally consists of risk/benefit information to help patients decide whether to have a device used on them and to allow patients to become aware of potential problems with the device. Patient labeling may also include descriptive information about the device, types of patients for whom the device would not be a good choice, alternative therapeutic choices, and any other information to enable the person to make an informed decision about the device.[141]

Based on the Patient Brochures I reviewed and the letter from K.S. Crawford to Plaintiffs' Counsel documenting the final versions and approval dates of the Patient Brochures for the pelvic floor products,[142] there was one Patient Brochure relevant to PROSIMA, with an Ethicon approval date of 11/9/2009.[143]

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[137] ETH.MESH.00372653 at 655: December 20, 2007, FDA Letter to Bryan Lisa, Ethicon, RE: K071512/S01.
[138] ETH.MESH.00748459 at 469: May 9, 2008, Response to FDA Letter on K071512: PROLIFT and PROLIFT+M Systems.
[139] ETH.MESH.00190766 at 790: June 2005 Project Mint Charter Presentation.
[140] FDA Guidance on Medical Device Patient Labeling, April 19, 2001.
[141] *Id.*
[142] May 21, 2012, Letter: In Re Pelvic Mesh/Gynecare Litigation – CT 291.
[143] ETH.MESH.03906001-020: Patient Brochure, copyright 2011, titled "What you should know about Pelvic Organ Prolapse – stop coping, start living," Approval Date: 11/9/2009 (Per May 21, 2012, Letter from K. S. Crawford to Plaintiffs' Counsel).

The Patient Brochure for the PROSIMA device is false and misleading for the reasons discussed following. Ethicon failed to disclose in the brochure many of the same issues it failed to disclose to the FDA and physicians. For example, Ethicon fails to provide notice to the patients that there is no evidence that the PROSIMA is superior to the native tissue repair and that the PROSIMA carries additional and enhanced risks. In addition, the Patient Brochure suffers from the same lack of full disclosure of risks and complications as the IFU – for example, that erosions may require multiple surgeries, that pain, incontinence and dyspareunia may be chronic and permanent. There is a lack of fair balance, with the tag line, "stop coping, start living" and the multiple deceptive pictures (i.e., six pictures, all suggesting contentment, normal function [dancing, content husband/male partner], or physician confidence) delivering an overriding message of a successful outcome.

***OPINION #3: Labeling for the PROSIMA Systems Was Inadequate***

Product labeling is a cornerstone of risk management. Its purpose is to provide the user with the information necessary to use the product safely and effectively, including to make decisions about the appropriateness of the device as a treatment option for a particular patient.[144] For these reasons, a device manufacturer must implement labeling changes in a timely manner as soon as possible after notice of any issues that may impact the safety or effectiveness of the device.[145] The globally recognized industry standard for prescription devices, such as the PROSIMA System, is for the product IFU to contain the information necessary for the treating physician to use the device safely and effectively for its intended use; this information includes any expected and foreseeable side effects, warnings, contraindications, precautions (including those related to materials incorporated into the device that are carcinogenic or toxic, or could result in untoward reaction of the patient), and any associated measures to be taken and limitations of use.[146]

In my professional opinion, based on my review of the PROSIMA labeling history, IFU and Patient Brochure, Ethicon deviated from the standard of care required of a medical device manufacturer by marketing this device without a critical device component: adequate labeling. Critical information was missing from both the professional labeling (IFU) and the patient labeling (Patient Brochure). Specifically, Ethicon marketed the PROSIMA without adequate instructions for use, notably, without adequate warnings, precautions, and information for implanting surgeons and patients about the extent and likelihood of potential risks, the difficulty of mesh removal and associated morbidity should mesh removal be required, the potential permanency and life-altering implications of certain risks of mesh implantation, and the lack of a proven, favorable benefit-to-risk ratio for this device compared to native tissue repair. As Ethicon's testimony has made clear, the company knew of the various risks associated with the PROSIMA that were not included in the IFU and patient labeling information.[147]

***OPINION #4: Adequate Informed Consent for Surgical Implantation of the PROSIMA Device Was Not Possible Because Labeling Was Inadequate.***

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[144] Songara RK et al. Need for Harmonization of Labeling of Medical Devices: A Review. J Adv Pharm Technol Res 2010;1(2):127-144.
[145] Bryan Lisa deposition, 12/19/11, 293:12-294:18.
[146] Final Document: The Global Harmonization Task Force. Label and Instructions for Use, September 16, 2011 (Supersedes previous version, June 3, 2005).
[147] Piet Hinoul deposition, 4/5/12, 140:11-141:2; 298:14-299:21.

The Patient Brochure for the PROSIMA Systems failed to serve the expected intent of patient labeling, i.e., to provide factual and balanced information to aid the patient in deciding whether to have the device implanted or to select an alternative treatment option for management of pelvic organ prolapse. Patient labeling conveyed a false and misleading impression by its failure to inform patients of meaningful, relevant information about potential risks and consequences of PROSIMA mesh implantation. In my professional opinion, the Patient Brochure for the PROSIMA failed to meet the industry standard of care for patient labeling.

Because of the deficiencies in both the professional labeling (IFU) and the Patient Brochure, physicians and patients lacked information critical to a frank discussion of the potential benefits and also the potential risks of device implantation, including the likelihood, the severity, and the potentially life-altering impact of certain risks. A manufacturer's belief that physicians and/or patients may be aware of certain risks associated with its product is not a justification for a failure to reveal material facts and consequences. The manufacturer is in the best position to know the safety and effectiveness profile of its product; certain information available to the manufacturer is either not available or not readily available to the implanting surgeon. Accordingly, the globally recognized industry standard is that the manufacturer is responsible for ensuring that both the physician and the patient, through professional labeling and patient labeling, where employed, have the information necessary to enable the patient to decide the treatment option best for her and to give fully-informed consent. In my professional opinion, patients implanted with the PROSIMA could not be adequately consented and give fully-informed consent as a result of Ethicon's failure to provide adequate professional and patient labeling.

## VI. BASES FOR OPINION #5 --- FDA ACTIONS: SERIOUS COMPLICATIONS ASSOCIATED WITH TRANSVAGINAL PLACEMENT OF SURGICAL MESH FOR PELVIC ORGAN PROLAPSE

### A. 2008 *FDA PUBLIC HEALTH NOTIFICATION*

By 2008, FDA was aware of potential safety issues with urogynecologic surgical mesh products because of information received through multiple sources. These sources included (1) postmarket surveillance of the MAUDE database for medical device reports (MDRs), (2) concerns raised by the clinical community and citizens, and (3) the published literature.

A search of the MAUDE database in 2008 showed that more than 1000 MDRs had been received from 2005-2007. These were reports of complications from nine surgical mesh manufacturers of surgical mesh devices used to repair POP and SUI.

As a result of these findings, FDA issued a *Public Health Notification* (PHN) in October 2008 informing clinicians and their patients of these findings, with recommendations on how to mitigate risks and how to counsel patients titled **"Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence."**[148]

According to the 2008 PHN:

[148] FDA *Public Health Notification*: Serious Complications Associated with Transvaginal Placement of Surgical Mesh in Repair of Pelvic Organ Prolapse and Stress Urinary Incontinence, Issued October 20, 2008.

"The most frequent complications included erosion through vaginal epithelium, infection, pain, urinary problems, and recurrence of prolapse and/or incontinence. There were also reports of bowel, bladder, and blood vessel perforation during insertion. In some cases, vaginal scarring and mesh erosion led to a significant decrease in patient quality of life due to discomfort and pain, including dyspareunia. Treatment of the various types of complications included additional surgical procedures (some of them to remove the mesh), IV therapy, blood transfusions, and drainage of hematomas or abscesses. Specific characteristics of patients at increased risk for complications have not been determined. Contributing factors may include the overall health of the patient, the mesh material, the size and shape of the mesh, the surgical technique used, concomitant procedures undertaken (e.g. hysterectomy), and possibly estrogen status.

**Recommendations** Physicians should:

- Obtain specialized training for each mesh placement technique, and be aware of its risks.
- Be vigilant for potential adverse events from the mesh, especially erosion and infection.
- Watch for complications associated with the tools used in transvaginal placement, especially bowel, bladder and blood vessel perforations.
- Inform patients that implantation of surgical mesh is permanent, and that some complications associated with the implanted mesh may require additional surgery that may or may not correct the complication.
- Inform patients about the potential for serious complications and their effect on quality of life, including pain during sexual intercourse, scarring, and narrowing of the vaginal wall (in POP repair).
- Provide patients with a written copy of the patient labeling from the surgical mesh manufacturer, if available."[149]

### B. *2011 FDA SAFETY COMMUNICATION*

In January 2011, the FDA completed another search of the MAUDE database for the 2008-2010 timeframe. This new search identified an additional 2874 MDRs for urogynecologic surgical mesh, with slightly more than half associated with POP repairs. On July 13, 2011, based on the 2008-2010 MAUDE database search and the FDA epidemiologic systematic literature review, the FDA issued a *Safety Communication* titled **"UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse"**[150] to inform the medical community and patients that:

(1) serious complications associated with surgical mesh for vaginal repair of POP are **not rare** [Emphasis added.] (contrary to what was stated in the 2008 *PHN*), and

(2) it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair.

According to the *Safety Communication*:

"Although it is common for adverse event reporting to increase following an FDA safety communication, we are concerned that the number of adverse event reports remains high. From

[149] *Id.*
[150] FDA *Safety Communication*: UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse, Issued July 13, 2011.

2008 – 2010, the most frequent complications reported to the FDA for surgical mesh devices for POP repair include mesh erosion through the vagina (also called exposure, extrusion or protrusion), pain, infection, bleeding, pain during sexual intercourse (dyspareunia), organ perforation, and urinary problems. There were also reports of recurrent prolapse, neuro-muscular problems, vaginal scarring/shrinkage, and emotional problems. Many of these complications require additional intervention, including medical or surgical treatment and hospitalization."[151]

Additionally:

"In order to better understand the use of surgical mesh for POP and SUI, the FDA conducted a systematic review of the published scientific literature from 1996 – 2011 to evaluate its safety and effectiveness. The review showed that transvaginal POP repair with mesh does not improve symptomatic results or quality of life over traditional non-mesh repair. The FDA continues to evaluate the literature for SUI surgeries using surgical mesh and will report about that usage at a later date."

In particular, the literature review revealed that:

- Mesh used in transvaginal POP repair introduces risks not present in traditional non-mesh surgery for POP repair.
- Mesh placed abdominally for POP repair appears to result in lower rates of mesh complications compared to transvaginal POP surgery with mesh.
- There is no evidence that transvaginal repair to support the top of the vagina (apical repair) or the back wall of the vagina (posterior repair) with mesh provides any added benefit compared to traditional surgery without mesh.
- While transvaginal surgical repair to correct weakened tissue between the bladder and vagina (anterior repair) with mesh augmentation may provide an anatomic benefit compared to traditional POP repair without mesh, this anatomic benefit may not result in better symptomatic results.

The FDA's literature review found that **erosion** of mesh through the vagina is the **most common and consistently reported mesh-related complication** from transvaginal POP surgeries using mesh. Mesh erosion can require multiple surgeries to repair and can be debilitating for some women. In some cases, even multiple surgeries will not resolve the complication. **Mesh contraction** (shrinkage) is a **previously unidentified risk** of transvaginal POP repair with mesh that has been reported in the published scientific literature and in adverse event reports to the FDA since the Oct. 20, 2008 *FDA Public Health Notification*. Reports in the literature associate mesh contraction with vaginal shortening, vaginal tightening and vaginal pain. Both mesh erosion and mesh contraction may lead to severe pelvic pain, painful sexual intercourse or an inability to engage in sexual intercourse. Also, men may experience irritation and pain to the penis during sexual intercourse when the mesh is exposed in mesh erosion."[152] (Emphasis added.)

"The complications associated with the use of surgical mesh for POP repair have not been linked to a single brand of mesh."[153]

The *Safety Communication* also provided a list of recommendations for health care providers and

[151] *Id.*
[152] *Id.*
[153] *Id.*

patients to consider for before and after transvaginal POP repair with mesh.[154]

**N.B.:** In reference to FDA's above-noted statement that "[m]esh contraction (shrinkage) is a previously unidentified risk," it is important to note that this risk was known to Ethicon in November 2006, yet Ethicon did not disclose this information to FDA during the Prosima 510(k) review. Specifically, Ethicon knew there were issues with the Prolift from the perspective of some experts, including Professor Jacquetin, who created the Prolift product or was the leader of the team that created the product: erosions and shrinkage[155] In fact, the erosion and shrinkage problems were significant enough that Ethicon was trying to find a way to address them.[156] According to Dr. Robinson's testimony, both the mesh and the surgical technique can be factors leading to erosion.[157] As regards shrinkage, it was believed the responsibility of the mesh was more established. and "further to the expert's discussion, it was speculated that Ultrapro could be (not is) a solution for this problem, which is less common but can be more severe than erosion."[158]

Moreover, the known problem with shrinkage was a specific topic of discussion at the "Ethicon Expert Meeting: Meshes for Pelvic Floor Repair" on February 23, 2007.[159] The record notes that Professor M. Cosson remarked that "Polypropylene meshes might not be improvable in terms of shrinkage, we may need a completely new material."[160]

The fact that FDA did not learn about this risk until after the October 2008 *FDA Public Health Notification* emphasizes the importance of the manufacturer's responsibility for compliance with the Medical Device Reporting requirements. Additionally, FDA's public health and safety communications in both 2008 and 2011 support my previously-stated opinion that, had FDA been apprised of the adverse event issues about which Ethicon was aware prior to the submission of the PROSIMA 510(k) number K063562, FDA would not have cleared the PROSIMA for marketing without adequate clinical evaluation.

### C. 2011 MEETING OF OBSTETRICS AND GYNECOLOGY DEVICES ADVISORY COMMITTEE AND JANUARY 4, 2012, FDA UPDATE

Finally, in September, 2011, as a result of the above-discussed findings, FDA convened a meeting of the Obstetrics and Gynecology Devices Advisory Committee to discuss "Surgical Mesh For Treatment Of Women With Pelvic Organ Prolapse And Stress Urinary Incontinence." Based on the September 2011 Obstetrics-Gynecology Devices Panel meeting as well as assessment of Medical Device Reports (adverse event reports) submitted to the FDA and evaluation of the published literature, FDA announced in a January 4, 2012, Update, that it is "considering the recommendation that urogynecologic surgical mesh used for transvaginal repair of pelvic organ prolapse (POP) be reclassified from Class II to Class III."[161]

Further, FDA advised in the January 2012 Update that it continued to assess the safety and

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[154] *Id.*
[155] Dr. David Robinson deposition, 3/14/2012. 447:10-448:15.
[156] Dr. David Robinson deposition, 3/14/2012, 451:17-24
[157] Dr. David Robinson deposition, 3/14/2012, 449: 20-24
[158] Dr. David Robinson deposition, 3/14/2012, 450:19-451:16.
[159] ETH.MESH.02017152: Ethicon Expert Meeting: Meshes for Pelvic Floor Repair, February 23, 2007, Minutes.
[160] ETH.MESH.02017152 at 153: Ethicon Expert Meeting: Meshes for Pelvic Floor Repair, February 23, 2007, Minutes.
[161] FDA UPDATE 01/04/2012: Urogynecologic Surgical Mesh Implants.

effectiveness of urogynecologic surgical mesh devices through a number of sources, including the published literature, epidemiological research on safety and effectiveness of surgical mesh, collaborations with professional societies and other stakeholders to fully understand the postmarket performance of urogynecologic surgical mesh devices and the occurrence of signs and symptoms associated with specific adverse events, and collecting and reviewing all available information about currently marketed urogynecologic surgical mesh devices.[162]

Additionally, on January 3, 2012, FDA issued 88 postmarket study orders to 33 manufacturers of urogynecologic surgical mesh for POP, including Ethicon. These orders mandate postmarket surveillance studies ("522 studies") and require the manufacturers to submit study plans to FDA to address specific safety and effectiveness concerns related to the surgical mesh devices for POP.[163]

### D. ETHICON'S DECISION TO WITHDRAW PROSIMA FROM THE U.S. MARKET

On January 3, 2012, Ethicon received an order from FDA under section 522 of the Federal Food, Drug, and Cosmetic Act to conduct a postmarket surveillance study of the PROSIMA Systems. FDA advised Ethicon that the PROSIMA was subject to postmarket surveillance under section 522 because it is a class II device that meets two of the required criteria: 1) Its failure would be reasonably likely to have serious adverse health consequences, specifically, to cause mesh erosion (i.e., organ perforation), severe pain, and fistula formation and 2) the PROSIMA is intended to be implanted in the body for more than one year.[164] Ethicon was required to submit a plan to conduct the required surveillance, after which FDA would determine whether the plan would "result in the collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health."[165] FDA noted its concern about potential safety risks as evidenced by adverse events reported to FDA and in the published literature and also was concerned about the published literature indicating lack of added clinical benefit compared to non-mesh repair.

FDA recommended that Ethicon conduct a randomized clinical trial (RCT) or prospective cohort study that would compare the PROSIMA to a control (e.g., transvaginal urogynecologic surgery without use of mesh) through 3 years of follow-up. In lieu of one of these recommended study designs, Ethicon could choose to develop a new sponsor registry or RCT/cohort study nested within a registry to address the public health questions posed by the 522 order. Ethicon was required to submit its plan within 30 days of receipt of the order.[166]

Ethicon announced on June 5, 2012, that it would withdraw PROSIMA and three other of its mesh implants from the U.S. market. Ethicon "stressed that the move was not a recall, but was based on the products' commercial viability 'in light of changing market dynamics, and is not related to safety or efficacy.'"[167] The company stated it had requested approval from the FDA to stop "commercializing" the devices and that sales of the devices would be halted worldwide.[168]

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[162] *Id.*
[163] *Id.*
[164] ETH.MESH.02658539: January 3, 2012, FDA Letter to Ethicon RE: Postmarket Surveillance (PS) Study: PS120044.
[165] *Id.*
[166] *Id.*
[167] Johnson & Johnson Unit to Halt Urinary Implants, by Katie Thomas, June 5, 2012, *The New York Times*.
[168] J&J Tells Judge It Will Stop Sales of Vaginal Implants, by Alex Nussbaum and Jef Feeley, June 5, 2012, *Bloomberg*.

By removing the product from the market, Ethicon avoided performing the required postmarket surveillance. Ethicon advised surgeons that it was not necessary to inform their PROSIMA patients of the market withdrawal or for PROSIMA patients to take any action. At no time did Ethicon share with the public its internal knowledge of known deficiencies related to the PROSIMA, as discussed previously in this report.

### E. FDA RECLASSIFIES VAGINAL MESH FOR POP REPAIR TO CLASS III AND REQUIRES PMA APPLICATION

On January 4, 2016, FDA issued two final orders to manufacturers and the public to strengthen the data requirements for transvaginal mesh products for pelvic organ prolapse repair, such as the PROSIMA. These products were reclassified from Class II, moderate-risk devices, to Class III, high-risk devices. In future, manufacturers will be required to submit a premarket approval (PMA) application and undergo the rigorous PMA pathway to demonstrate safety and effectiveness prior to approval (not clearance) to market of such devices. Thus, if Ethicon were to seek to market the PROSIMA today, the company would be required to conduct the appropriate clinical study(ies) and demonstrate safety and effectiveness and a favorable benefit-to-risk ratio or the product would not be allowed to reach the market.

***OPINION #5: Ethicon Failed to Act First in the Interest of Patient Safety When It Decided to Remove the PROSIMA From the Market.***

In my professional opinion, marketing of the PROSIMA should have been abandoned before the product was ever launched, but because it was marketed, once Ethicon determined it would remove the product from the market, the company should have acted much more quickly. Documentation in Ethicon's files shows that Ethicon made the decision to exit the market prior to receiving FDA's feedback on its proposed plan.[169] In fact, the company initiated the development of an exit plan in case it was needed in a February 7, 2012, Strategic Business Team Meeting.[170] Hence, when Ethicon received FDA's response on April 2, 2012,[171] which advised Ethicon that its plan lacked information needed for FDA to complete its review, the company should have been prepared to act immediately in the interests of patient safety to remove the product. Instead, Ethicon waited until May 9th to inform the FDA of its intention to discontinue sales of the PROSIMA and another month (June 5, 2012) to inform physicians. While this may not seem to be a long period of time, it is important to remember that during this time women continued to have a permanent device implanted – during which time Ethicon knew it was going to remove the device from the market and FDA had tentatively determined that safety and effectiveness of the PROSIMA had not been established. By delaying from April until June, Ethicon failed to follow its own Credo of putting doctors and patients first.

## VII. CONCLUSIONS

Based on my professional experience, knowledge, and training and my review, evaluation,

[169] Plaintiff's Exhibit 3190: Piet Hinoul Jun 26 notes.
[170] ETH.MESH.05597944: February 7, 2012, Strategic Business Team Meeting – Meeting Notes.
[171] ETH.MESH.08565137: April 2, 2012, Letter from FDA to Ethicon RE: Postmarket Surveillance Study Number PS120044.

integration, and synthesis of the information identified and discussed in this report, including also materials and scientific/medical literature listed and information presented in the exhibits to this report, is my professional opinion, to a reasonable degree of scientific and professional probability, that Ethicon violated those duties required of a reasonably prudent medical device manufacturer.

Ethicon failed to demonstrate that there was a favorable benefit-to-risk ratio for patients implanted with the PROSIMA. For example, there were underlying issues calling into question the reliability of the clinical data, internal concerns and negative feedback from key opinion leaders (KOLs), complications not associated with native tissue repair, and concerns about use of this product by the target customer: "generalists." The labeling for PROSIMA was incomplete and misleading due to multiple labeling issues, including inadequate directions for use, notably, inadequate warnings and information about potentially serious, permanent and life-altering risks. Ethicon failed to follow the standards it created for releasing the PROSIMA onto the market. If Ethicon had followed its own internal standards related to the safety and performance of this device, PROSIMA would never have been marketed. The product is no longer on the market.

As a consequence of these multiple failures, Ethicon marketed a product that violated safety and ethical standards. Both the physicians using the PROSIMA System and the patients in whom these devices were used lacked the necessary information to make an informed decision about the risks versus the benefit of using this device instead of an alternative method of treatment. Accordingly, the standard of care for the protection of the rights, safety, and welfare of patients was violated, thus disrupting the process and the protections that exist specifically to safeguard the public health.

I reserve the right to amend or supplement this Report in the event that additional pertinent information becomes available or additional issues are raised in reports of other experts.

Peggy Pence

Peggy Pence, PhD, RAC, FRAPS

February 1, 2016

Date

# EXHIBIT 2

# Peggy C. Pence, PhD, RAC, FRAPS

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## *PROFESSIONAL SUMMARY*

Dr. Pence offers over 40 years of experience in the research and development of traditional pharmaceutical and biotechnology-derived therapeutic products and medical devices, including in vitro diagnostics. Dr. Pence began her career at Eli Lilly and Company in 1970 in basic immunology research and later transitioned to clinical development and regulatory affairs. She subsequently held key project and clinical management positions at several emerging-growth companies, namely the U.S. start-up of Serono Laboratories, Triton Biosciences (acquired by Berlex Laboratories, Inc.), and Amgen, Inc. In 1992, Dr. Pence founded a consulting firm that was incorporated in 1995 as Symbion Research International, a full-service contract research organization. She has been President and Chief Executive Officer since that time. Dr. Pence is also Chief Executive Officer of Illuminostics, LLC, which she co-founded in January 2012 for the purpose of providing medical imaging services both for clinical trials and also to aid in the diagnosis and monitoring of disease in medical practice.

Over the course of her longstanding career, Dr. Pence has worked with over 80 companies and over 90 drugs, biologics, and medical devices spanning multiple therapeutic areas. She has broad experience in regulatory affairs and strategic planning, nonclinical testing, and all phases of clinical trials. Dr. Pence has enjoyed success in leading development programs for a number of novel products and has designed and managed numerous clinical studies, from first-in-man to pivotal studies to support marketing applications. She established, staffed, and directed the Clinical Quality Assurance and Document Control department at a leading biotechnology company, Amgen, Inc. She has directed collaborative clinical programs with foreign affiliates to reduce overall clinical development time and costs, and enhance quality and usability of data globally for marketing applications. Dr. Pence has served as the U.S. Agent or authorized representative for FDA (Food and Drug Administration) matters for medical device, pharmaceutical, and biopharmaceutical companies. She has prepared numerous regulatory submissions and consulted with the FDA concerning INDs, NDAs, BLAs, IDEs, 510(k)s, and PMAs. She has guided and coordinated product development activities from process development through marketing plans. Therapeutic areas of experience include neurology, neuropsychology, oncology, hematology, infectious disease, rheumatology, nephrology, respiratory disorders, women's health, metabolic and growth disorders, gastroenterology, burns, wound healing, and ophthalmology.

Among her accomplishments, Dr. Pence has consulted for a multinational pharmaceutical company to develop strategy and implement a global clinical data management system and also for a leading software company to develop information management solutions for the pharmaceutical and biotechnology industries. Dr. Pence has been instrumental in assisting a number of companies (both emerging-growth companies and established industry leaders) to evaluate current operations and implement new processes and procedures to achieve greater efficiency and ensure compliance with current regulations.

Dr. Pence earned her undergraduate degree in Microbiology from Louisiana Tech and her PhD in Toxicology from Indiana University. She is an active industry speaker and educator and has developed and is the instructor for two graduate-level courses for the California State University system: "Clinical Trials and Quality Assurance" and "Clinical Trials Project Management: Managing Clinical Trials." Dr. Pence founded and chaired the Drug Information Association (DIA) Biotechnology Subgroup and chaired 10 consecutive DIA workshops on biotechnology from 1991 through 2001. Dr. Pence holds the U.S. Regulatory Affairs Certification (RAC) designation and has served on the Regulatory Training Course Faculty, DIA, and as an instructor for the Orange Country Regulatory Affairs Discussion Group (OCRA) for candidates for Regulatory Affairs Certification. Dr. Pence is a RAPS (Regulatory Affairs Professionals Society) Fellow (FRAPS), a peer-reviewed credential for which she was selected based on her experience, contributions, and leadership in the regulatory profession. She serves on the Board of Directors or Advisory Board for multiple organizations.

## *PROFESSIONAL EXPERIENCE*

**Founder, President and Chief Executive Officer | Symbion Research International, Inc.**
Newbury Park, California | 1995-Current

- Responsible for establishing and maintaining corporate culture, ethical standards, and vision.
- Determine corporate direction and oversee business development.
- Responsible for executive decisions regarding systems implementation, policies, and procedures.
- Provide expert advice to clients regarding regulatory, nonclinical, and clinical development matters and product development strategic planning.
- Serve as regulatory liaison with FDA for client companies.
- Provide expert advice and represent clients for FDA meetings.
- Provide guidance to clients to achieve resolution of non-compliance issues identified during FDA inspection.
- Function as director of product development for virtual companies.
- Directly oversee and participate in clients' pivotal development programs (i.e., maintain a "hands-on" approach).
- Provide leadership and counsel to Symbion teams assigned to clients' projects.
- Design clinical protocols and programs, proposing innovative methods as appropriate.
- Organize and chair (as appropriate) multi-center Investigators'/Study Coordinators' Meetings.
- Direct the conduct, management, monitoring, data management, analysis, and reporting of clinical trials.
- Perform critical review of key regulatory submissions to ensure highest quality and successful submissions.
- Evaluate clinical operations of client companies and recommend solutions to increase effectiveness; accordingly, revise and develop Standard Operating Procedures (SOPs).
- Perform quality assurance audits of pivotal clinical trials.
- Conduct training programs in regulatory affairs, Good Clinical Practice, and Good Laboratory Practice.
- Experience with novel therapeutic products, including oncolytic viruses, tissue-engineered products, interferons, monoclonal antibodies, neurotrophic factors, growth factors, peptides, and toxins, as well as new chemical entities; Class I, II, and III medical devices, including in vitro diagnostics; innovative drug delivery systems; and combination products. Clinical indications studied include a variety of cancer types, neurological conditions, pain management, cognitive disorders, diabetes, infectious diseases, including HIV/AIDS and other sexually transmitted diseases, respiratory disorders, gastrointestinal disorders, hepatitis, burns, chronic wounds, and women's health concerns.

**Co-Founder and Chief Executive Officer | Illuminostics, LLC**
Newbury Park, California | 2012-Current

- Establish and maintain corporate culture, ethical standards, and vision.
- Determine corporate direction and oversee business development.
- Responsible for executive decisions regarding systems implementation, policies, and procedures.
- Provide leadership and counsel to Illuminostics team projects.
- Oversee development and revision of Standard Operating Procedures (SOPs).

**President | Product Development Consulting**
Newbury Park, California | 1992-1995

- Designed and conducted clinical programs, Phases I to III.
- Established new clinical functions or departments for client companies, including Standard Operating Procedures (SOPs) and systems.

## *PROFESSIONAL EXPERIENCE (Continued)*

- Evaluated, prepared study reports, and summarized nonclinical and clinical data for NDA submission.
- Evaluated and re-engineered product development processes for implementation of new information technology systems, assessing and planning conversion strategy.
- Served as key member of clients' product development teams, providing expert advice on regulatory and product development matters and strategic planning.
- Prepared regulatory submissions (including clinical protocols and amendments; Investigator's Brochures; initial IND submissions, IND amendments and annual reports; 510(k)s, PMAs; Clinical Study Reports, etc.).
- Consulted for a multinational pharmaceutical company to develop strategy and implement a global clinical data management system.
- Provided expert advice to leading software company to develop information management solutions for the pharmaceutical and biotechnology industries.

**Amgen, Inc. | Thousand Oaks, California**
**Associate Director, Clinical Quality Assurance and Document Control**
**Manager, Clinical Operations**
**Manager, Clinical Studies**
1988-1992

- Key member of product development teams for consensus interferon and wound-healing growth factors.
- Responsible for preparation or critical review of significant parts of IND submissions.
- Designed and directed clinical programs for consensus interferon and "first-time-in-man" studies of recombinant wound-healing growth factors; consensus interferon program led to licensing approval for treatment of hepatitis C virus infection.
- Awarded management responsibility for ongoing gamma interferon clinical programs.
- Established and staffed clinical quality control and assurance department and functions, developed procedures and systems, and achieved major targeted deadline (for human granulocyte colony stimulating factor [G-CSF] program) within first three months of operation.
- Managed staff responsible for adverse event and concomitant medication coding across all clinical programs worldwide.
- Directed the establishment and functioning of a Clinical Records and Information Center for the storage, organization, protection, and management of clinical trial documents across all clinical programs, including an International Records Library.
- Directed the development of a Case Report Form (CRF) tracking system for all clinical programs, including operating procedures and reporting capabilities.
- Developed comprehensive training curriculum for clinical development staff.
- Responsible for developing and administering annual and five-year research and development plans and budgets.
- Managed staff of over 40 clinical research professionals.
- For all functions, met all targeted deadlines and achieved all departmental and divisional goals at a level of 125% to greater than 150%.

**Manager, Therapeutics Projects | Triton Biosciences, Inc.**
Alameda, California | 1986-1988

- Project manager accountable for all planning, direction, scheduling, monitoring and control of assigned projects, including recombinant interferon-beta and transforming growth factor, from process development through marketing plans.
- Organized and chaired formal project reviews with co-development company and also internal project team; provided company officers with regular progress reports, through both written documents and oral briefings.

## *PROFESSIONAL EXPERIENCE (Continued)*

- Prepared master plan for development of a new purification procedure and formulation; assured project control and adherence to the plan to achieve target date for completion.
- Directed compilation from three separate databases and writing of clinical safety assessment for over 500 patients for FDA submission.
- Responsible for evaluation of therapeutic and commercial potential of new chemical entity.
- Key member of strategy-setting team for therapeutic projects.
- Managed major extramural nonclinical research programs; designed and implemented nonclinical toxicology, pharmacology, and efficacy studies.

**Pharmaceutical Research Manager | Serono Laboratories, Inc.**
Randolph, Massachusetts | 1983-1986

- Responsible for the design and execution of nonclinical and clinical development programs in two major product areas: interferon-beta and human growth hormone, both native and recombinant.
- Awarded management responsibility for ongoing trials of bovine thymus peptide product (thymostimulin) in AIDS and AIDS-Related Complex (ARC) patients.
- Took over a mismanaged trial, cleaned it up, and administered FDA's inspections of this trial (including both sponsor and investigator) to successful outcomes.
- Successfully designed and completed Phase I trial, inspected by FDA subsequent to above-noted inspections; inspection completed in approximately two hours, resulting in inspector's pronouncement that this was one of the best audit results he had seen.
- Directed development of collaborative clinical programs with foreign affiliates, notably the United Kingdom, France, Israel, and Italy, to reduce corporate's overall clinical development costs and enhance quality and usability of data globally for marketing applications.
- Designed and implemented four Phase I and II trials, designed and developed Phase III multi-center trials in six indications, including ocular and sexually-transmitted infectious diseases, cervical intraepithelial neoplasia, and growth hormone deficiency. Organized and chaired four multi-center Investigators'/Study Coordinators' Meetings.
- Conceived and successfully proposed Phase III clinical strategy to FDA to reduce the time to NDA submission by approximately one year.
- Recommended a clinical study that led to an application for use patent.
- Implemented a clinical study in collaboration with the National Institutes of Health, which was applauded as a potential landmark study and eventuated letters of commendation both from senior company management and the study investigators.
- Collaborated with overseas manufacturing facilities (Israeli, Italian, and Swiss affiliates) to develop task completion schedules and resolve process development issues; personally arranged characterization and validation studies and coordinated activities with affiliate and contract laboratories to assure timely completion.
- FDA liaison (telephone contacts, formal presentations and meetings).
- Prepared Supplemental New Drug Application and subsequently prepared a presentation of the data therein for FDA Advisory Committee meeting, at FDA's invitation.
- Wrote protocol and SOPs for enzyme-linked immunosorbent assay to detect antibody development in patients treated with interferon-beta.
- Coordinated validation of an antibody assay (for human growth hormone patients) by diagnostics affiliate to effect a 50% savings in assay costs compared to extramural laboratory charges.
- Prepared summary of all non-U.S. safety data (interferon-beta) for submission to regulatory agencies in support of marketing applications; recognized by corporate and affiliate offices for value of contribution.
- Directed the activities of four clinical research professionals and two secretaries.

## *PROFESSIONAL EXPERIENCE (Continued)*

**Eli Lilly and Company | Indianapolis, Indiana**
**Medical Information Administrator, Regulatory Affairs**
1982-1983
**Educational Leave of Absence to Complete Doctoral Research**
1980-1982
**Cosmetic Chemist, Research and Development | Elizabeth Arden Division**
1974-1977
**Associate Microbiologist, Immunology Research Laboratory**
1970-1974

- Broad exposure to the planning, drug development, and decision-making processes at a leading pharmaceutical corporation.
- Responsible for monitoring Phase III and IV clinical trials for original and supplemental NDA submissions.
- Contributed to preparation of clinical protocols, CRFs, and Investigator's Brochures.
- Collaborated with biostatisticians, computer programmers, and data analysts to establish data entry and verifications systems.
- Prepared a variety of regulatory submissions, including quarterly reports to the newly approved NDA for Humulin®, the first product of recombinant DNA origin to be approved for sale.
- Acquired experience in multiple product categories: antiemetic, narcotic analgesic, anti-inflammatory, and antiparkinsonism drugs.
- Supervised staff of three non-exempt personnel.
- As cosmetic chemist, developed complete line of powder products, troubleshot for pilot plant and production, worked closely with marketing and claims substantiation departments; conducted skin physiology research.
- As associate microbiologist, participated in the design and execution of *in vivo* and *in vitro* experiments to develop a reliable and reproducible screening assay for identifying agents affecting cell-mediated immunity; acquired tissue culture and laboratory animal experience.

## *EDUCATION*

**Doctor of Philosophy (PhD), Toxicology, Pharmacology minor**
Indiana University (Medical School campus) | Indianapolis, Indiana | 1983
**Thesis: Comparative effects of cannabinoids alone and in combination with other centrally acting drugs.**
Doctoral research conducted at the Eli Lilly Laboratory for Clinical Research (Indianapolis, Indiana):

- Planned and personally executed all aspects of three clinical pharmacology and toxicology studies, from protocol conception to subject selection to Clinical Study Report.
- Synthetic cannabinoid Cesamet® studied in two of these trials approved by FDA, December 1985; prepared report on drug abuse liability trial results for FDA Drug Abuse Advisory Committee, which report was central to Committee's recommendation (1983) for scheduling under the Controlled Substances Act.

**Bachelor of Science (BS), *Magna cum Laude,* Microbiology**
Louisiana Polytechnic University (Louisiana Tech) | Ruston, Louisiana | 1969

## ACADEMIC HONORS

| | |
|---|---|
| 2008 | Selected for Bossier High School Alumni Hall of Fame \| Bossier City, Louisiana |
| 1982 | Member of Sigma Xi, The Scientific Research Society |
| 1982 | Third place, annual Sigma Xi competition for graduate research presentations \| Indiana University School of Medicine |
| 1981 | Second place, annual Sigma Xi competition for graduate research presentations \| Indiana University School of Medicine |
| 1966 | Valedictorian, Bossier High School \| Bossier City, Louisiana |

## PROFESSIONAL CERTIFICATION OR DESIGNATION

- U.S. Regulatory Affairs Certification (RAC)
- Regulatory Affairs Professionals Society Fellow (FRAPS) | 2009

## CURRENT PROFESSIONAL MEMBERSHIPS

- Regulatory Affairs Professionals Society (RAPS)
- The Food & Drug Law Institute (FDLI, corporate membership)
- Drug Information Association (DIA)
- International Society for Pharmacoepidemiology (ISPE)
- Southern California Biomedical Council (SoCalBio, corporate membership)
- Orange County Regulatory Affairs Discussion Group (OCRA)

## SELECTED HONORS AND AWARDS

| | |
|---|---|
| October 6, 2010 | OCRA and San Diego Regulatory Affairs Network (SDRAN) Certificate of Appreciation for Presentation: "Getting Your Product to Market in the New Regulatory Environment," San Diego, California |
| June 17, 2010 | OCRA Certificate of Appreciation for Dedication to OCRA, Irvine, California |
| June 16-17, 2010 | OCRA Certificate of Appreciation: Speaker (Moderator), 13th Annual FDA-OCRA Educational Conference, "The Business of Compliance," Irvine, California |
| August 1, 2009 | OCRA Certificate of Appreciation: US RAC Study Group Presenter, Brea, California |
| June 9-10, 2009 | OCRA Certification of Appreciation: Award Recipient, OCRA Volunteer Appreciation 2009 for Support of OCRA, Irvine, California |
| November 19, 2008 | OCRA Certificate of Appreciation: Global Clinical Trials, Carlsbad, California |
| September 6, 2008 | OCRA Certificate of Appreciation: US RAC Study Group Presenter, Brea, California |

## ACADEMIC APPOINTMENTS

| | |
|---|---|
| 2012-2013 | Developed Course and Instructor, California State University, Fullerton, Biology 538: Clinical Trials Project Management: Managing Clinical Trials |
| 2011-present | Developed Course and Part-time Faculty Member, California State University, Channel Islands, Biology 516: Clinical Trials and Quality Assurance |

## *ACADEMIC APPOINTMENTS (Continued)*

| | |
|---|---|
| Spring 2009 | Instructor/Advisor, California State University, Channel Islands, Master of Science in Biotechnology Program Team Projects, Subject: Development Pathway and Issues for Probiotics as Therapeutics |

## *BOARDS OF DIRECTORS AND ADVISORY BOARDS*

| | |
|---|---|
| 2012 - present | The Food and Drug Law Institute (FDLI), *Update* Editorial Advisory Board |
| 2009 - 2013 | Biotechnology and Health Programs Advisory Board, California State University, Channel Islands |
| 2009 | Clinical Trials Certificate Program Advisory Board, California State University Program for Education and Research in Biotechnology (CSUPERB) |
| 2008 - 2009 | Biotechnology Advisory Committee, California State University, Channel Islands |
| 2007 - present | Board of Directors, CompassioNow (formerly CareNow Foundation) |
| 2006 – 2008 | Scientific Advisory Board, CytoDyn, Inc. |
| 2003 – 2005 | Board of Directors, CytoDyn, Inc. |
| 2003 | Board of Directors, VCBio |
| 1989-present | Board of Directors, The Iraida Foundation |
| 1987 | First Editorial Advisory Board, *BioPharm Manufacturing* |

## *SELECTED PROFESSIONAL CONTRIBUTIONS*

| | |
|---|---|
| September 24, 2013 | "Quality Executive Leadership Series: FDA and Industry Executives Working Together to Improve Quality," Workshop between U.S. Food and Drug Administration and Industry Executives, Irvine, California |
| 2009 | Southern California Biomedical Council (SCBC) Gold Coast Event Planning Committee |
| 2009 | Co-Founder & Meetings Chairperson, Venture Coast Life Science Innovators (VCLSI) |
| 1994 - 1996 | Drug Information Association (DIA) Annual Meeting Program Committee, Biotechnology Track<br>- *Session Chairperson: Current Research Targets in Biotechnology Including Therapeutics and Therapeutic Vaccines, 1995* |
| 1994 | DIA Regional Steering Committee |
| 1993 - 1995 | DIA Steering Committee of the Americas |
| 1990's | Originator and Chair, Drug Information Association (DIA) Biotechnology Subgroup |

## *PUBLICATIONS*

- Robson MC, Phillips LG, Thomason A, Altrock BW, Pence PC, Heggers JP, Johnston AF, et al. "Recombinant human platelet-derived growth factor-BB for the treatment of chronic pressure ulcers." Ann Plast Surg 1992; 29: 193-201.
- Lemberger L, Rubin A, Wolen R, DeSante K, Rowe H, Forney R, Pence P. "Pharmacokinetics, metabolism and drug-abuse potential of nabilone." Cancer Treatment Reviews 1982; 9 (Supplement B): 17-23.

## *CONFERENCE CHAIRMANSHIPS*

| | |
|---|---|
| February 12-13, 2001 | 9th Annual Drug Information Association (DIA) Workshop, Program Co-Chairperson, "Biotechnology: Global Perspectives," Dana Point, California |
| May 6-7, 2000 | 8th Annual DIA Biotechnology Workshop, Program Co-Chairperson, "Biotechnology: Global Perspectives," Dana Point, California<br>- *Session Chairperson: "Biotechnology in Australia, Europe, and Japan"* |
| February 1-2, 1999 | DIA 7th Annual Biotechnology Workshop, Program Chairperson, "Biotechnology: Product Development for the New Millennium," Dana Point, California |
| February 5-6, 1998 | DIA 6th Annual Biotechnology Workshop, Program Chairperson, "Clinical Trials and Product Development in Biotechnology," Dana Point, California<br>- *Session Co-Chairperson: "Getting into the Clinic with Novel Products – DNA Vaccines and Gene Therapy"* |
| February 20-21, 1997 | DIA 5th Annual Biotechnology Workshop, Program Chairperson, "Clinical Trials in Biotechnology," Dana Point, California |
| January 29-30, 1996 | DIA 4th Annual Biotechnology Meeting, Program Co-Chairperson, "Regulatory Reform: Its Impact on Clinical Trials and Product Development in Biotechnology," Newport Beach, California<br>- *Session Chairperson: "Key Considerations for Regulatory/Clinical Development in the Current Industry Environment"*<br>- *Speaker: "Perspectives on the ICH GCP Guideline"* |
| January 30-31, 1995 | DIA 3rd Annual Biotechnology Meeting, Program Co-Chairperson, "Clinical Trials in Biotechnology," Newport Beach, California<br>- *Session Chairperson: "Optimizing Data Management for Emerging Biopharmaceutical Companies"* |
| June 6-7, 1994 | DIA Annual Meeting, Biotechnology Track Co-Chairperson |
| January 30-February 1, 1994 | DIA Annual Symposium on Biologics and Biotechnology, Program Co-Chairperson, "Clinical Trials in Biotechnology: Planning to Prevent the Pitfalls," Newport Beach, California<br>- *Session Chairperson: "Tactics for Execution"*<br>- *Speaker: "Performing with the Best Actors: Efficiency and Quality"* |
| May 19-21, 1993 | DIA Biotechnology Workshop, Program Chairperson, "Biotechnology: Meeting the Challenges of the 1990s," Boston, Massachusetts<br>- *Speaker: "Integrating CAPLAR/CANDA in the Product Development Process"* |
| November 20-22, 1991 | DIA Biotechnology Workshop, Program Chairperson, "Clinical Development of Biotechnology Products," Santa Monica, California<br>- *Speaker: "A Comprehensive Approach to Achieving Efficiency and Quality in Clinical Research"* |

## *SPONSORED SYMPOSIA*

| | |
|---|---|
| October 14, 2008 | PQC Consulting, Inc., and Symbion Research International, Inc., Co-Sponsored Symposium, "Good Clinical Practice and the Clinical Study Process," Lead Instructor: Peggy Pence, PhD, RAC, Los Angeles, California |
| October 15, 2003 | Symbion Research International, Inc., and Interface International Consultancy, Ltd., Co-Sponsored Symposium: "How to CE Mark a Medical Device," Instructor: Brian James, PhD, FBIRA |

## *SPONSORED SYMPOSIA (Continued)*

| | |
|---|---|
| November 5, 2002 | Symbion Research International, Inc., and Interface International Consultancy, Ltd., Co-Sponsored Symposium: "European Regulations: Medical Devices, Drug-Device Combinations, Orphan Drugs and a Glance into the Future," Instructor: Brian James, PhD, FBIRA, La Jolla, California |
| November 4, 2002 | Symbion Research International, Inc., and Interface International Consultancy, Ltd., Co-Sponsored Symposia: "Drug-Device Combinations: A European Perspective" and "European Regulations: A Glance into the Future," Instructor: Brian James, PhD, FBIRA, Irvine, California |

## *SELECTED PRESENTATIONS*

| | |
|---|---|
| October 1, 2013 | "The Importance of Ethics - Postmarketing Challenges," Situation Room Speaker, 2013 RAPS Annual Conference: The Regulatory Convergence, Boston, Massachusetts |
| September 30, 2013 | "The Importance of Ethics - Premarketing Challenges," Situation Room Speaker, 2013 RAPS Annual Conference: The Regulatory Convergence, Boston, Massachusetts |
| August 1, 2009 | "Medical Device Submissions and Post-Approval Requirements for Medical Devices," Instructor for OCRA, US Regulatory Affairs Certification (RAC) Study Group |
| February 26, 2009 | "Finding New Medical Therapies: The R&D Process – Discovery Research through Post-Marketing," Guest Lecturer: Biology 601, Master of Science in Biotechnology program, California State University, Channel Islands |
| November 19, 2008 | "The Use of Databases and Electronic Data Capture in Clinical Studies," Speaker (Co-Presenter with Diane Ascoli) and Panel Member: OCRA - San Diego Regulatory Affairs Network (SDRAN) Joint Meeting, "Global Clinical Trials: An Overview and Update," Carlsbad, California |
| September 6, 2008 | "Device Submissions: PMA, 510(k) (21 CFR Regulations: Devices - 807, 809 & 814)," Instructor for OCRA, US Regulatory Affairs Certification (RAC) Study Group |
| June 10, 2008 | "Drugs/Biologics Product Development: Understanding the Complexities, Managing the Risks," Guest Lecturer: Biology 601, Master of Science in Biotechnology program, California State University, Channel Islands |
| March 27, 2008 | "Personalized Medicine, Regulatory Perspective," Speaker and Panel Member: Southern California Biomedical Council (SoCalBio) Networking Forum: "Personalized Medicine Are We There Yet," Westwood, California |
| April 24, 2007 | "Successful Product Submissions," (Interactive) Audio Conference: Thompson Publishing Group, Co-Presenter with Dr. Kathryn Kimmel |
| April 17, 2007 | "Clinical Data Management: Annual Good Clinical Practices Review," Corporate Program, San Diego, California |
| November 15, 2006 | "Risk-Benefit Analysis in Clinical Development," BioFlorida Annual Conference, Gainesville, Florida |
| June 6, 2006 | "Clinical Data Management: Case Report Form Fundamentals," Corporate Program, San Diego, California |
| March 2, 2006 | "Clinical Data Management: Annual Good Clinical Practice (GCP) Training Workshop," Corporate Program, San Diego, California |
| November 8, 2005 | "Navigating the Drug Development Pipeline from Innovation to Market," Presentation to the Women in Health Administration of Southern California |
| May 20, 2004 | "Integrating Regulatory, Clinical and Marketing Efforts into a Profitable Reimbursement Strategy," Audioconference: FDA News, Co-Presenter with Jennifer Murray and Chris Waugh |
| October 28, 2003 | "Good Clinical Practice (GCP) and Regulatory Training Workshop," Corporate Program, Westlake Village, California |
| October 20, 2003 | "Safari of Life, My Personal Journey: Bench to Business," Presentation to Forum for Women Entrepreneurs, San Diego, California |

## *SELECTED PRESENTATIONS (Continued)*

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|---|---|
| June 24, 2003 | "Good Clinical Practice (GCP) and Regulatory Training Workshop," Corporate Program, Westlake Village, California |
| December 1-3, 1993 | Drug Information Association (DIA) Pharmaceutical Document Management, Program Speaker, San Francisco, California |
| September 1, 1993 | "Good Clinical Practices and Effective Study Monitoring Workshop," Corporate Program, San Diego, California |
| September 23, 1992 | "The Oracle Biotechnology Seminar: Flexible Information Management Within A Regulated Industry," An Executive Seminar with Dr. Peggy Pence, Oracle Corporation, Santa Clara, California |

## *SELECTED CONTINUING EDUCATION*

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|---|---|
| September 30-October 2, 2013 | 2013 Regulatory Affairs Professionals Society (RAPS) Annual Conference: "The Regulatory Convergence," Boston, Massachusetts |
| June 6, 2013 | "Skadden Seminar for Pharmaceutical, Biotechnology and Medical Device Companies: A Dialogue on Regulation, Litigation and Shareholder Activism," Costa Mesa, California |
| November 1, 2012 | "RAPS/FDA Case for Quality Forum," Irvine, California |
| April 24-25, 2012 | The Food and Drug Law Institute's 55th Annual Conference, Washington, D.C. |
| November 2, 2011 | "How to Avoid the Escalation of Enforcement Activities," Orange County Regulatory Affairs Discussion Group (OCRA), Irvine, California |
| October 19, 2011 | "Corporate Compliance: Understanding the Current Enforcement Climate," OCRA and San Diego Regulatory Affairs Network (SDRAN) Joint Meeting, San Diego, California |
| September 26-27, 2011 | The Food and Drug Law Institute's Advertising and Promotion Conference for the Pharmaceutical, Medical Device, Biologic and Veterinary Medicine Industries, Washington, D.C. |
| February 8-10, 2011 | Medical Design and Manufacturing (MD&M) West 2011 Conference, Anaheim, California |
| October 7, 2010 | Town Hall Meeting, FDA's Center for Devices and Radiological Health (CDRH), Irvine, California |
| October 6, 2010 | "Getting Your Product to Market in the New Regulatory Environment," OCRA and SDRAN Joint Meeting, San Diego, California |
| June 16-17, 2010 | "The Business of Compliance," 13th Annual FDA-OCRA Educational Conference, Irvine, California<br>- *Session Moderator: "Enforcement Activities of Significance"* |
| May 19, 2010 | California Life Sciences Day at the State Capitol, Sacramento, California |
| April 28, 2010 | "Risk Management for Regulated Industries," OCRA, Irvine, California |
| March 10, 2010 | "Navigating CAPA: Smooth Sailing with Continuous Improvement," OCRA, Irvine, California |
| February 8-10, 2010 | "Marketing a Medical Device in the US" and "The Future is Now: Anticipating a New Era of FDA Enforcement, Parts I & II," MD&M West 2010 Conference, Anaheim, California |
| January 26, 2010 | "Regulatory Strategies for Biologics Development," SDRAN Annual Meeting & Presentation, San Diego, California |
| November 19, 2009 | "Adoption Process of Novel Technologies: Challenges and Solutions," Drug Safety Executive Council (DSEC) Webinar |
| November 6, 2009 | "Convergence, Creating BioSynergy," BioFlorida's 12th Annual Conference, Orlando, Florida |
| October 21, 2009 | "European Regulation on Advanced Therapies," The Weinberg Group, Webinar |
| September 30, 2009 | "ANDA vs. 505(b)(2) – When and Why?," The Weinberg Group, Webinar |

## *SELECTED CONTINUING EDUCATION (Continued)*

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|---|---|
| September 14-16, 2009 | Regulatory Affairs Professionals Society (RAPS) Annual Conference & Exhibition, Philadelphia, Pennsylvania |
| September 9, 2009 | "FDA's New Strategy on Enforcement: The Growing Perils of Inadequate Compliance," The Weinberg Group, Webinar |
| June 9-10, 2009 | "The Challenges of Ensuring Product Safety," 12th Annual FDA-OCRA Educational Conference, Irvine, California |
| May 27, 2009 | "Global Lessons in Developing Biosimilars," The Weinberg Group, Webinar |
| April 15, 2009 | "Pharmaceutical Development in Europe: Key Points to Consider," The Weinberg Group, Webinar |
| April 7-8, 2009 | 2009 Florida Medical Device Symposium, Florida Medical Manufacturer's Consortium, Inc., Tampa, Florida |
| January 29, 2009 | "Workshop on Accessing Government Funding for Bioscience Research," Southern California Biomedical Council (SoCalBio), Westwood, California |
| November 19, 2008 | "Global Clinical Trials: An Overview and Update," OCRA-SDRAN Joint Meeting, Carlsbad, California |
| September 19, 2008 | 10th Southern California Biomedical Council Investor Conference, Los Angeles, California |
| June 16, 2008 | Israel Life Sciences Day at BIO 2008, La Jolla, California |
| June 11-12, 2008 | "Regulatory Affairs: Expanding to Global Horizons," 11th Annual FDA-OCRA Educational Conference, Irvine, California |
| February 8, 2008 | "Striving for Regulatory Success in a Changing Environment," Hyman, Phelps & McNamara, PC, Medical Device Seminar, Newport Beach, California |
| June 11-12, 2007 | "Celebrating 10 Years of Regulatory Affairs Education," 10th Annual FDA-OCRA Educational Conference, Irvine, California |
| November 30-December 1, 2006 | 2006 Global Summit on AIDS and the Church: Race Against Time, Saddleback Church Campus, Lake Forest, California |
| November 14-15, 2006 | "Intersections: Converging Fields, Emerging Opportunities," BioFlorida Annual Conference, Gainesville, Florida |
| August 13-18, 2006 | XVI International AIDS Conference, Toronto, Canada |
| November 29-30, 2005 | HIV/AIDS Conference, Saddleback Church Campus, Lake Forest, California |
| June 4-5, 2003 | "Understanding the Changing Landscape," 6th Annual FDA-OCRA Educational Conference, Irvine, California |
| March 12-13, 2001 | "Opportunities for Drug Development and Discovery in Women's Health," Drug Information Association (DIA), Washington, D.C. |
| October 25, 1999 | "Annual Update on Women's Health Research: Discoveries and Implications," Ninth Annual Scientific Advisory Meeting, Society for the Advancement of Women's Health Research, Washington, D.C. |
| March 22-23, 1999 | "Contracting with Site Management Organizations," Barnett International Conference Group, Philadelphia, Pennsylvania |
| June 25-29, 1995 | "The Changing Regulatory Environment and Its Impact on Global Healthcare," DIA 31st Annual Meeting, Orlando, Florida |
| May 20-25, 1995 | Ninth BIO International Biotechnology Meeting & Exhibition, San Francisco, California |
| December 7-8, 1993 | "In Vitro Diagnostics – A Regulatory Update," Regulatory Affairs Professionals Society (RAPS) 1993 Educational Programs, San Francisco, California |
| July 11-15, 1993 | "Global Drug Development: Focus on the Americas," DIA 29th Annual Meeting, Chicago, Illinois |
| April 12-16, 1993 | Association of Biotechnology Companies 7th International Biotechnology Meeting & Exhibition, Research Triangle Park, North Carolina |

## *SELECTED CONTINUING EDUCATION (Continued)*

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|---|---|
| June 8-11, 1992 | "Pharmaceutical Development: National and Transnational Dynamics," Drug Information Association, San Diego, California |
| February 27, 1992 | "Micro Planner X-Pert" Training, Amgen Corporate Information Technologies, Thousand Oaks, California |
| Circa 4th Quarter 1991 | "Preparing for an FDA-GCP Audit," Barnett International Seminar, prepared and presented for Amgen, Inc. |
| January 10-14, 1990 | "Clinical and Experimental Approaches to Dermal and Epidermal Repair: Normal & Chronic Wounds," 3rd International Symposium on Tissue Repair, Miami, Florida |
| May 18-20, 1988 | "Project Management in the Pharmaceutical Industry," The Institute for Applied Pharmaceutical Sciences, Los Angeles, California |
| January 16-17, 1986 | "Introduction to Laboratory Techniques: Biochemical Separations," Cook College, Continuing Professional Education, Rutgers University, New Brunswick, New Jersey |
| November 14-15, 1985 | "Gene and Its Product," Cook College, Office of Short Courses and Professional Training, Rutgers University, New Brunswick, New Jersey |
| July 11, 1984 | "Ophthalmic Toxicology," The Center for Professional Advancement, East Brunswick, New Jersey |

## *SELECTED COMMUNITY AND CIVIC ACTIVITIES*

| | |
|---|---|
| 2012 | Charter Member, Rotary E-Club of One World |
| 2006 – 2011 | Rotary International, The Rotary Club of Westlake Village<br>- *International Committee and Meals on Wheels Administrator, 2008*<br>- *Program Chair, 2009 – 2010*<br>- *Club Service Chair and Board of Directors, 2010 – 2011* |
| 2002 | Ageless for Life Radio Show, Health and Fitness Speaker and Consultant, Chicago, Illinois |
| 2001 – 2002 | Los Angeles World Affairs Council, International Circle |
| 1983 | Instructor, City/County Marijuana Education Program, Indianapolis, Indiana |
| 1983 | Senior Editor and Pharmacology Consultant, Health Alert Publishing Company, Indianapolis, Indiana |
| 1982 – 1984 | Invited Speaker on substance abuse, to a variety of parent, student, and professional groups |
| 1982 – 1983 | Volunteer Staff by Invitation, Fairbanks Hospital, specializing in the treatment of alcoholism and drug addiction, Indianapolis, Indiana |